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To be or not to be obese: impact of obesity on lymphatic function

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Obesity is the leading cause of morbidity and mortality, with more than one-third (36.5%) of US adults estimated to be suffering from this chronic multifunctional disease. Obesity imposes serious difficulty on exercising, which may exacerbate the risk of obesity-related complications including cardiovascular disease, stroke, type 2 diabetes and various types of cancer (Segula, 2014). Obesity impacts practically every organ system, particularly the cardiovascular and metabolic systems that have been studied extensively. A plethora of studies have investigated the consequence of obesity on vascular dysfunction, with a prime focus on strategies to improve cardiovascular and metabolic comorbidities linked with obesity. The pathological effect of obesity on the lymphatic system, however, is far less understood. Recent studies (Greene *et al.* 2012; Arngrim *et al.* 2013) have suggested that obesity can lead to lymphoedema, resulting in reduced ability to clear macromolecules within the interstitial space by the lymphatic system, and cause compromised operating of antigen presenting cells and anomalous lymph node structure. These lymphatic injuries can further intensify the pathological process of obesity-related diseases in other organ systems through amplifying inflammatory responses. With the obesity epidemic being a global issue and showing no sign of fading, it is important to understand the impact of obesity on lymphatic dysfunction, and discover a viable therapeutic solution to reverse such dysfunction.

While it has been widely investigated and confirmed that obesity causes lymphatic dysfunction, the prospect of reversing these deleterious effects with nutritional or pharmacological interventions has remained unexplored. To address this gap in our knowledge, in a recent study published in *The Journal of Physiology* Nitti *et al.* (2016) investigated the association of lymphatic dysfunction with obesity and the possibility of reversing the dysfunction through weight loss. The authors hypothesized that obesity would critically impair the lymphatic system and through diet-controlled weight loss, the function of lymphatic system could be restored. To test their hypothesis, Nitti and colleagues used a diet-induced obesity mouse model, where the experimental animals were divided into obese, weight-loss and lean (control) groups. First and foremost, the authors reported that weight gain correlated negatively with the collecting lymphatic pumping frequency in obese mice. Furthermore, these mice displayed a significantly lower number of cutaneous LYVE-1$^+$ lymphatic vessels (1.88-fold) when compared to lean mice, and a significant increase in the lymphatic vessel area, showing that the lymphatic vessels are dilated in obese mice. LYVE-1 is a lymphatic endothelium antigen that has been successfully utilized in diagnostic pathology. The negative effects of obesity-induced perivascular inflammation on vascular endothelial dysfunction and vascular complications have been widely reported. In line with these findings, the authors demonstrated an association between weight gain and accretion of inflammatory cells within a 50 μm radius of cutaneous lymphatic vessels, as evaluated with co-localization of CD45 (a pan-leukocyte marker) and LYVE-1. Nitric oxide (NO), produced by the inducible nitric oxide synthase (iNOS) is a recognized controller of the collecting lymphatic pumping function. Subsequently, inflammatory cells being a major source of iNOS, the perilymphatic expression of iNOS was examined. The authors showed a distinct accumulation of iNOS$^+$ cells gathering around lymphatic vessels in obese mice and a significant positive correlation with weight gain was reported.

A subgroup of the obese mice was then subjected to a calorie restriction diet, which resulted in rapid weight loss and reduction in adipose tissue deposition, to levels similar to those of the lean controls. Concomitantly, metabolic parameters (total cholesterol, triglycerides, HDL, serum glucose, insulin) were significantly improved after weight loss. To further delve into the mechanisms responsible for the beneficial effects of weight loss on lymphatic dysfunction, the authors evaluated the accumulation of inflammatory cells close to cutaneous lymphatic vessels. It is believed that perilymphatic inflammation induced by obesity may play a significant role in obesity-induced lymphatic dysfunction and that weight loss may reverse this occurrence. After verifying the perilymphatic inflammation by measuring T cells (CD3$^+$) and macrophages (F4/80$^+$) within a 50 μm radius of lymphatics (LYVE-1$^+$), the authors demonstrated that weight loss was able to reverse the elevated T cell (4.4-fold increase) and macrophage (1.9-fold increase) numbers back to lean control levels. In addition, the authors observed a 3-fold increase in iNOS$^+$ perilymphatic cells upon weight gain, with macrophages (CD11b$^+$) being the major source of iNOS. This phenomenon was reversed with weight loss, resulting in a significant decrease (2.54-fold) in perilymphatic iNOS$^+$ cells compared to obese mice sustained on a high-fat diet (HFD), thus further confirming the beneficial effect of weight loss of reducing the inflammatory response.

Finally, Nitti *et al.* (2016) analysed the lymphatic vessel function in obese mice and the subsequent effect of weight loss on lymphatic function. Upon performing Evans Blue lymphangiography, obese mice showed an increase in leakiness of initial and collecting lymphatics. Further functional analyses of obese mice revealed a more than 2-fold decrease in collecting lymphatic pumping capacity, a 15-fold decrease in the percentage migration of dendritic cells to the regional lymph nodes, and a 3-fold decrease in clearance of macromolecules in obese mice when compared to the lean controls. Overall, weight loss induced by transferring obese mice from a HFD to a normal chow diet (NCD) was able to successfully reverse several lymphatic dysfunctions induced by obesity, such as lymphatic leakiness, reduced lymphatic vessel density, reduced cutaneous lymphatic collecting vessel pumping rate and reduced lymphatic macromolecule clearance. Most of the lymphatic function parameters

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measured in the weight loss group were indistinguishable from lean controls, confirming the advantages of weight loss to alleviate lymphatic function.

Overall, the authors have demonstrated that weight loss through diet restriction can reverse several obesity-induced lymphatic dysfunctions, suggesting that the pathological changes in obese lymphatic system can be reversed and metabolic changes can be restored. These findings are of particular relevance, since exercise training showed a similar effect on obesity-related lymphatic dysfunction (Geoffrey *et al.* 2016). However, it is important to note that, the reversal of lymphatic dysfunction may not be solely due to the weight loss. As described by Nitti *et al.* (2016), HFD not only contributed to the weight gain and increase in adipose tissue deposition, but also contributed to metabolic changes, such as the increase in total cholesterol, triglycerides, HDL, LDL, and serum insulin. In addition, obese mice developed insulin resistance and showed elevated serum glucose levels during the study. After switching to a NCD for 8 weeks, the metabolic changes in weight loss mice returned to baseline level, while they still had significantly more adipose deposition when compared to lean controls. Although the correlation between weight gain and lymphatic dysfunction is well elucidated in this study, the reversal of obesity-related lymphatic dysfunction may be multifactorial and further investigations on adipose deposition and metabolic changes are warranted.

In conclusion, the current study indicates that lymphatic dysfunction is associated with obesity and the dysfunction could be significantly reversed by diet-controlled weight loss. Importantly, the study highlights the association between obesity and the accumulation of inflammatory (T cells and macrophage) perilymphatic cells. Altogether the findings suggest that a calorie-restricted diet, with subsequent weight loss, is a clinically relevant treatment alternative for obesity-related lymphoedema patients. Although limited, the current study by Nitti *et al.* (2016) reinforces the causative and critical role of obesity in lymphatic dysfunction, and sheds light on the likelihood of reversing it through weight loss.

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Additional information

Competing interests

None declared.

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