MOH FOCUS

Compression therapy in veno-lymphatic disorders: effects on pain and inflammation

Pain and inflammation in veno-lymphatic disorders

Veno-lymphatic disorders are frequently associated with pain and inflammation. Accumulated fluid significantly impacts cellular behavior within the affected region and induces subsequent pathological changes (immune cell infiltration, adipose accumulation and tissue fibrosis) [1]. There is still poor understanding of the physiopathology of pain and inflammation symptoms associated with veno-lymphatic disorders. This MOH Focus is looking closer into the physiopathology of these symptoms and how they can be relieved or lowered through the application of medical compression systems.

Chronic venous disease (CVD)

Venous stasis, causing local hypoxia and abnormal (lower) shear stress (the frictional force generated by the blood flow in the veins) leads to the release of inflammatory mediators from endothelial cells. These inflammatory mediators are theorized to sensitize and activate venous nociceptors, causing the characteristic pain of CVD[2,3,4]. CVD patients without risk for neuropathy from other causes, had a decreased function in nerve fibers [2]. This could be additional evidence for the negative effects of CVD on nerve fibers.

Lymphedema (LE)

Both experimental and clinical studies spanning several decades have implicated inflammation as a critical component in the physiopathology of lymphedema [5]. Chronic interstitial fluid stasis promotes activation of chronic inflammatory pathways, adipose deposition and further decrease lymphatic function, thereby activating a feed-forward mechanism leading to tissue hypoxia and disease progression [6].

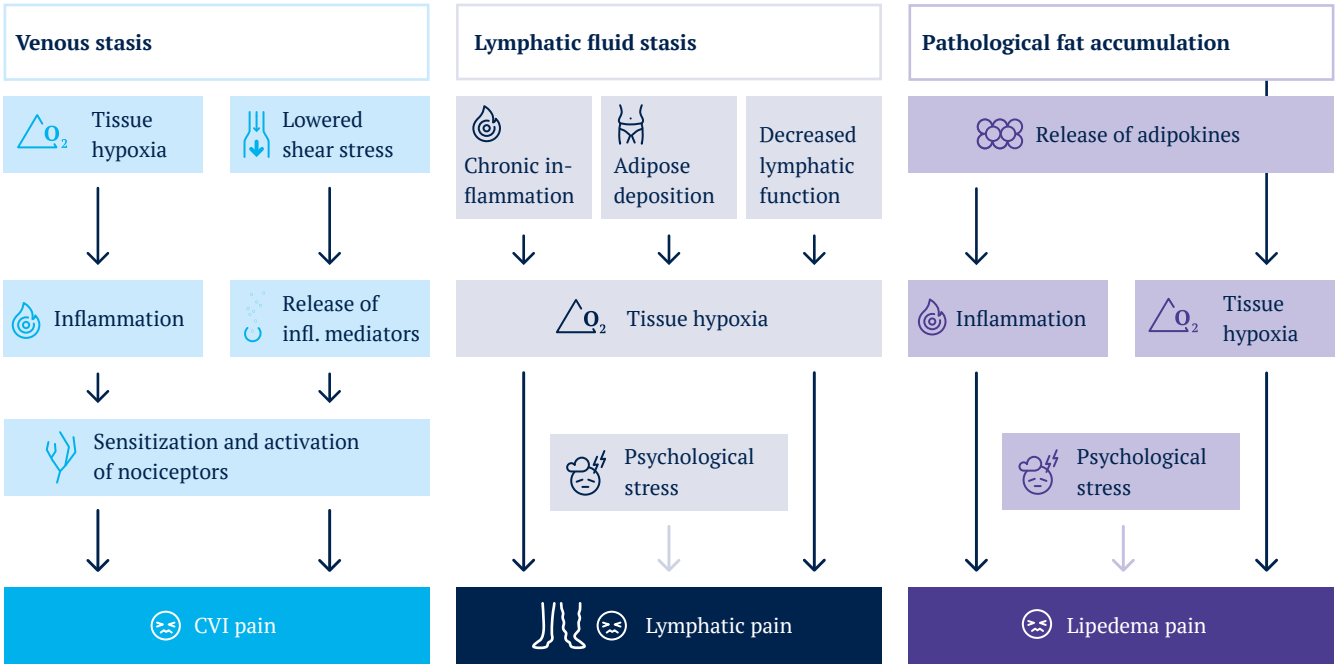
Although pain is not as frequently associated with LE like with lipedema, more recent studies have shown, that there is a significant association between LE, pain, and the level of distress experienced by patients [7].

Newer findings further suggest that one component of LE pain may be related to the increased fluid accumulation and/or associated inflammatory responses [8].

Lipedema (LiE)

The etiology of pain in lipedema is unclear, though histology findings of inflammation and hypoxia may be contributing elements [9]. Recent findings, that identify a chronic low-grade state of inflammation and tissue hypoxia as the most plausible explanations for the pain in LiE patients, support this hypothesis [10].

Fat cells are only able to expand with increased vascular growth. The vessels' inability to keep pace with the expanding adipose tissue may lead to the observed tissue hypoxia. The hypoxic conditions in the LiE tissue further lead to an increased expression of hypoxia-inducible factors (HIF1a), inducing inflammation of the adipose tissue. Recently it has come to understand that chronic pain can also be (co-)triggered by stress or even personal conditions. This is another interesting aspect regarding a possible explanation for the etiology of pain [10].



Benefits of compression therapy in veno-lymphatic disorders

Medical compression reduces venous and lymphatic stasis and inflammatory mediators, thereby counteracting the main reasons for the development of pain and inflammation symptoms in patients with veno-lymphatic disorders.

Chronic venous disease (CVD)

Medical compression leads to an increase of shear stress in the microcirculation and to a release of anti-inflammatory mediators from the endothelial cells [11,12]. It also enhances venous emptying, reduces pain and edema [4], and can, by decreasing ambulatory venous hypertension in the area, counteract the chronic inflammation in the tissues and finally aid healing processes.

Lymphedema (LE)

In addition to other effects, compression therapy also acts on trophic changes by releasing anti-inflammatory mediators, minimizing areas of interstitial fibrosis [13].

The pressure differential (increase in interstitial fluid pressure) induced by the compression therapy reduces capillary filtration, increases the microcirculation blood flow and facilitates interstitial fluid movement and lymph drainage, thereby reducing limb volume [14].

The anti-fibrotic and anti-inflammatory effects of the compression therapy might thereby contribute to counteract the progression of lymphatic dysfunction and to lower LE related pain.

Lipedema (LiE)

In the light of recent findings explaining the etiology of pain and inflammation in LiE patients in more details, it can be imagined that the basis for prescribing compression therapy might not be the edema reduction anymore, but rather the reduction of pain by the frequently demonstrated anti-inflammatory effects of compression therapy on the subcutaneous tissue [10].

Although the use of medical compression brings only a small reduction in tissue volume (5–10%) in various studies, it does lessen tenderness (pain on pressure) and feelings of tightness in the limbs [15]. Studies demonstrate that medical compression wearing results in a significant reduction in oxidative stress, a finding that also points to improved microcirculation in the subcutaneous tissues [10].

Compression effects

Direct compression effects	· Enhanced venous emptying and lymphatic drainage · Increased shear stress in microcirculatory blood flow · Reduced capillary filtration · Reduced areas of interstitial fibrosis
Secondary compression effects	· Edema reduction due to less capillary filtration and better lymphatic drainage · Release of anti-inflammatory mediators from shear stress activated endothelial cells · Less tissue hypoxia due to better microcirculation
Beneficial effects of compression	· Reduced CVD symptoms* and LE symptoms** · Reduced DVT risk · Less inflammation causes less pain

* leg heaviness, varicose veins, edema, skin changes, ulceration ** leg heaviness, tightness, edema, recurring infections, fibrosis

Take-home message

Veno-lymphatic disorders are associated with pain & inflammation.
Compression therapy has a positive impact on veno-lymphatic function and is a standard, non-invasive treatment option for all veno-lymphatic diseases.
Scientific data also shows direct evidence for an analgesic & anti-inflammatory effect of compression therapy in veno-lymphatic disorders.

References (1) Jiang, et al. "Lymphatic Dysfunction, Leukotrienes, and Lymphedema". Annu Rev Physiol.; 80: 49–70 (2018). (2) Orhurhu, et al. "Management of Lower Extremity Pain from Chronic Venous Insufficiency: A Comprehensive Review". Cardiol Ther 10:111–140 (2021). (3) Raffeto et al. "Mechanisms of Lower Extremity Vein Dysfunction in Chronic Venous Disease and Implications in Management of Varicose Veins". Vessel Plus. doi:10.20517/2574-1209.2021.16 (2021). (4) Chen et al. "Matrix Metalloproteinases in Remodeling of Lower Extremity Veins and Chronic Venous Disease". Prog Mol Biol Transl Sci.; 147: 267–299 (2017). (5) Ly et al. "Inflammatory Manifestations of Lymphedema". Int. J. Mol. Sci., 18, 171 (2017). (6) Dayan et al. "Lymphedema: Pathogenesis and Novel Therapies". Annu. Rev. Med. 69:263–76 (2018). (7) Mobarakeh et al. "Combined decongestive therapy and reduction of pain and heaviness in patients with breast cancer-related lymphedema". Supportive Care in Cancer, 27:3805–3811 (2019). (8) Fitzgerald et al. "Lymphatic Pain in Breast Cancer Survivors". Lymphatic Research and Biology; Volume 00, Number 00 (2021). (9) Herbst et al. "Standard of care for lipedema in the United States". Phlebology Vol. 36(10) 779–796 (2021). (10) Bertsch et al. "Lipoedema: a paradigm shift and consensus". JWC Consensus Document Vol 29, Sup. 2, No 11 (2020). (11) Partsch et al. "Compression for leg wounds. British Journal of Dermatology". 173, pp359–369 (2015). (12) Beidler et al. "Inflammatory cytokine levels in chronic venous insufficiency ulcer tissue before and after compression therapy". J Vasc Surg;49:1013-20 (2009). (13) Bergmann et al. "Conservative treatment of lymphedema: the state of the art". J Vasc Bras.;20:e20200091 (2021). (14) Haesler et al. "Evidence Summary: Managing lymphoedema: compression therapy". Wound Practice and Research; Volume 24 Number 4 (2016). (15) Kruppa et al. "Lipedema—Pathogenesis, Diagnosis, and Treatment Options". Dtsch Arztebl Int; 117: 396–403 (2020).