Lymphoedema in bariatric patients

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Morbid obesity and lymphedema

- Morbid obesity: definition and co-morbidities
- Mechanisms of lymphedema

- Obesity and lymphedema: is there a link?
- What is the evidence for a reciprocal relationship?

- Pathophysiology of lymphedema in bariatric patients

- Could improvement/reversal also be reciprocal?
Adipose tissue

Adipose tissue is made up of
- Adipocytes and preadipocytes
- Various stromal cells
- Resident and infiltrating immune cells
- Extensive endothelial network

It is an endocrine organ involved in:
- Insulation
- Energy depot, lipid storage, regulation of glucose balance, ...
- Regulation of several biological processes of the metabolic, endocrine, immune system, and inter-organ communication

Lymphatics: Function, in relation to Adipose Biology

- Lymphatic vessels
  - intimate spatial association with adipose tissue (*mouse model: no lymph nodes → no fat pad*)
  - Uptake: fluid, macromolecules, cells
  - lipid absorption & transport (gut)
  - trafficking of immune cells

Morbid obesity: definition and co-morbidities

BMI: weight in kg / height in m²
• < 18.5 kg/m² = underweight
• 18.5 - 24.9 = normal
• 25 - 29.9 kg/m² = overweight
• ≥ 30 kg/m² = obese
• ≥ 40 kg/m² = morbidly obese

Obesity-related disease impacts all organ-systems:
• Cardiovascular diseases: hypertension, pulmonary hypertension, left-sided heart failure → oedema, microangiopathies, CVI...
• Diabetes, metabolic syndrome, (metabolic diversity), hyperlipidemia, fatty liver
• Obstructive sleep apnoea → leg oedema
• Reduced life expectancy
• Lower HRQoL
• cancer
Morbid obesity and lymphedema: is there a link?

• Obesity itself: level/severity: does obesity lead to developing lymphedema?
• Triggering factors for a genotype with ‘chronic subclinical lymphedema’
• CVI: chronic venous insufficiency
• Does having lymphedema lead to becoming obese?
Morbid obesity and lymphedema: is there a link? **CVI?**

In obese people: ↗ increasing limb symptoms with increasing obesity

↗ Chronic venous insufficiency (CVI), even without anatomical evidence of venous disease (Duplex ...)

- Reduced venous return (from obstruction by abdominal fat, diaphragma less mobile)
- Increased dependency (limited mobility, sleep apnea: sleep upright)
- Reduced calf muscle pumping (inactivity, orthopaedic problems), ambulatory venous hypertension
- Changes in Starling forces (increased blood pressure, capillary filtration)
- Inflammatory changes, ulceration
CVI may be underestimated
CVI may be underestimated
Morbid obesity and lymphedema: is there a link? **Obesity**?

- Obesity itself: level/severity: 75% of morbidly obese pts have LyOed - 1/3 of sec. LyOed pts were morbidly obese (Fife 2008)
- Superobese individuals can develop lymphedema even without antecedent surgery or ‘injury’
- A body mass index **threshold** appears to exist between BMI 53 and 59 at which point lower extremity lymphatic dysfunction and lower extremity lymphedema occurs

- One retrospective level IV study of patients presenting to an obesity clinic found that approximately 1/3 of patients had abnormalities on lymphoscintigraphy
- NB. While imaging investigations might be of interest, they will not change the treatment plan.
Morbid obesity and lymphedema: is there a link? **Obesity**?

- In clinical practice, patients present with a mix of **comorbidities**: CVI, obesity, congestive heart failure, diabetes or insulin resistance +/- thyroid dysfunction, sleep apnea, lipoedema, impaired mobility, hypertension ... and they may take medication which increases the odds of developing oedema

- NB breast-cancer related lymphedema: risk factors: age, history of hypertension, degree of dissection, inflammation/infection, **obesity***: obesity increases lymphedema (reversible through weight loss)
Morbid obesity and lymphedema: is there a link? Occult lymphedema?

Lymphedema?

In obese people, leg oedema is common and multifactorial:
Self-reporting swollen legs: OR 1.8 in overweight group, OR 5 in obese people
Lymphedema = ‘silent’ primary, or secondary?
Cause not always clear cut, may be multifactorial
• Harder to confirm in early stages,
• Later stages: pos. Stemmer sign, fibrosis, elephantiasis, ...
• D.D. lipoedema
• Massive localized lymphedema (MLL)
Morbid obesity and lymphedema: MLL

Massive localized lymphedema (MLL):
Prevalence 1.3% in lymphoedema pts
(Fife 2008)

Figure 5. The epidermis has flattened the rete ridges overlying marked dermal oedema and a patchy lymphocytic infiltrate (H&E).

Imaging / MRI / CT
Expansion of fat tissue also into muscle, thickened skin, fibrosis of septae

Obesity independently decreases lymphatic function and vice versa

Hypotheses and observations:

- Impaired lymphatic function can lead to adipose deposition and obesity: resulting from both proliferation and hypertrophy of local adipocytes,
- and the resulting adipose depots are chronically inflamed and infiltrated by macrophages and lymphocytes.
Obesity-induced inflammatory changes in adipose tissue

Adipose tissue dysfunction:
• More and larger adipocytes
• Resident vs infiltrating macrophages
  T-cells, a.o. cells
• Angiogenesis
• Fibrosis
• Local and systemic (via portal system) chronic low-grade inflammation, modified biology of other organs (liver, lungs, cardiovascular…), insulin resistance

Obesity independently decreases lymphatic function

Hypotheses:

- Accumulation of interstitial fluid (incl. tissue accumulation of lipids, cholesterol) leads to a massive up-regulation of adipocyte differentiation genes and increased expression of adipokines (hormones produced by adipose tissues).

Adipose tissue expansion, impact on endothelium

Obesity independently decreases lymphatic function

The negative effects of obesity on lymphatic function may be **multifactorial** and dependent on changes in the extracellular matrix, inflammatory reactions, and direct injury to lymphatic endothelial cells.

Obese patients may therefore be at risk for lymphedema because they have compromised lymphatic function at baseline, have abnormal inflammatory responses that can negatively impact the lymphatic system, and have impaired ability to regenerate damaged lymphatics after injury.
Obesity independently decreases lymphatic function

Obesity and dietary changes can profoundly change **lymphatic function**:  

- $\downarrow$ interstitial fluid transport capacity (load > clearance)  
- Abnormal lymphatic vessel density, valves, pumping activity  
- Impaired trafficking of immune cells, including impaired dendritic (antigen presenting) cell migration to local lymph nodes  
- Abnormal lymph node architecture  
- Changes in lymphangiogenesis
Morbid obesity and lymphedema: pathophysiology

- HFD-induced obesity decreases lymphatic function by increasing perilymphatic inflammation, and altering LEC gene expression.
- Obesity downregulates expression of lymphatic markers in LECs.
- Reversal of diminished VEGFR-3 signaling may rescue this phenotype and improve lymphatic function.

HFD results in decreased lymphatic vascular density in obesity-prone mice (C57 mice)

Obesity results in accumulation of large lipid droplets around lymphatic vessels

- Obesity impairs lymphatic transport of macromolecules to draining lymph nodes

Obesity results in local tissue and perilymphatic inflammation
Inflammation in Chronic advanced lymphoedema

- Chronic interstitial fluid accumulation leads to adipose deposition, persistent inflammation, and fibrosis, often resulting in massive hypertrophy of the affected area...

- ...decreasing the potential for response to treatment, and

- associated with severe infections, functional disability, skin changes, psychosocial morbidity, even malignant transformation
Lymphedema in bariatric patients

Key points

Obesity results in perilymphatic inflammation and lymphatic dysfunction. The disturbances are reciprocal.

The good news:

**Aerobic exercise**, independent of weight loss,

- decreases perilymphatic inflammatory cell accumulation,
- improves lymphatic function and
- reverses pathological changes in gene expression in lymphatic endothelial cells.
Exercise decreases lymphatic leakiness and improves migration of dendritic cells (DCs) in obesity

- A, Evans Blue **microlymphangiography** in ears from lean, sedentary obese and exercised obese mice.

- White dotted circles correspond to the site of injection; red arrowheads show areas of lymphatic leakage; and red dotted circle represents possible expansion of lymphatic filling in exercise obese mice.

- B, **whole mount images** obtained from mouse ears following fluorescein isothiocyanate (FITC) lectin injection and **localizing lymphatic vessels** (podoplanin+; green), α-smooth muscle actin (α-SMA+; red), FITC-labelled injected lectin (green) and nuclei (DAPI).

- Note massive **extravasation** of dye in sedentary obese mice (yellow dotted line) and improvement in exercised obese mice.

Exercise, obesity and lymphatic function

Aerobic exercise improves collecting lymphatic vessel **pumping** in obesity

- A) representative line graphs demonstrating changes in ... hindlimb collecting lymphatic packet frequency (pumping) in lean, sedentary obese and exercised obese groups
- B) quantification of hindlimb collecting lymphatic packet frequency (pumping) in experimental groups

Lymphedema in bariatric patients

• Seems to be a to-way process, via multiple mechanisms
• Exercise training improves obesity-related lymphatic dysfunction
• Standard treatment for lymphedema is challenging in the morbidly obese patients
• Multidisciplinary approach → weight loss (> 5-10%) → health benefits
• Diet, physical activity, behavioral modification,
• Bariatric surgery
HAV EN GOD DAG!