Session 5: Lipedema / Lymphedema

Pathophysiology and genetics in lipedema

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What is lipedema? Diagnostic criteria...

Diagnostic criteria of lipedema (Wold, Hines, Allen, 1951)

1. Lipedema merely affects women and appears by the third decade of life
2. Bilateral and symmetrical fat deposits develop downward from the hips, while the feet are usually spared
3. Non-pitting edema
4. Affected subcutaneous regions are tender, painful and characterized by easy bruising
5. Resistance to diet and stimulation of backflow by the elevation of the extremities
6. Increased vascular fragility
Diagnosis of lipedema – a dilemma

Lipedema

Multiple Symmetric Lipomatosis (Madelung’s Disease/Syndrome)

Acquired partial lipodystrophy (APL, Barraquier-Simons-Syndrome)

Familial Partial Lypodystrophy (FPLD, Köbberling)

**Diagnostic criteria of lipedema (Wold, Hines, Allen, 1951)**

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Clinical presentation and classification of lipedema

**Stages**

1. Thickened subcutis, soft, with small, palpable nodules, skin surface still smooth
2. Thickened subcutis, soft, some larger nodules, skin surface uneven
3. Thickened subcutis, hardened, with large nodules, distorting fat deposition

**Types**

I) Buttock
II) Thigh
III) Entire lower limb
IV) Arm
V) Leg

*Type IV is often associated with type II or III.*

The Dutch diagnostic criteria for lipedema

A1+A2+A3+A4+A5

PLUS

(B6+B7) OR (C8+C9) OR (D10+D11) OR E12

In the absence of at most 2 of criteria A-E, the extra criteria F13 OR F14 also assure the diagnosis.
With all the diagnostic hurdles - is lipedema a disease at all?

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (WHO preamble to the Constitution).

<table>
<thead>
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<th>Reference</th>
<th>Year</th>
<th>Number of Subjects</th>
<th>The Aim of the Study</th>
<th>Quality of Life Questionnaire</th>
<th>Results</th>
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<td>[271]</td>
<td>2018</td>
<td>n = 329</td>
<td>To investigate the relationship between depression and lowered mobility</td>
<td>WHOCOL-BREF</td>
<td>Lower level of quality of life was associated with higher severity of symptoms, lower mobility, higher mobility</td>
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<table>
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<tr>
<th>Reference</th>
<th>Average Age of Onset</th>
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<th>Average Waiting Time for Diagnosis</th>
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<td>[23]</td>
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<td>38.3 years of age</td>
<td>18.3 years</td>
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<tr>
<td>[24]</td>
<td>16 years of age</td>
<td>31 years of age</td>
<td>15 years</td>
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The quality of life of people with lipedema was significantly lower than the average quality of life in the Dutch population; people with comorbidities had a lower quality of life.

What is lipedema?
An attempt to understand this disease/syndrome better by asking ...

- Is lipedema a lymphatic (vessel) disease?
- Is lipedema an inflammatory disease?
- Is lipedema a genetic disease?
- Is lipedema an endocrine disease?
- Is lipedema a psychosomatic disease?
No generally accepted evidence-based theory for the pathomechanism.
Morphological and functional alterations in adipose tissue in lipedema

Increased epidermis thickness in lipedema

No difference in fibrotic tissue/elastic fibers

Morphological and functional alterations in adipose tissue in lipedema

Adipocyte hypertrophy

Changes in adipocyte size distribution in lipedema

Blood vessels (ESAM1 staining, red)
Adipocytes (autofluorescence)

Is lipedema a genetic condition?

Schmeller et al.: inherited condition in up to 60% of patients

Child et al.: possible autosomal dominant inheritance with incomplete penetrance, exact genes were not identified

Harvey et al.: functional inactivation of PROX-1 leads to leaky lymphatics and obesity

Karkkainen et al. Mäkinen et al.: VEGFR3 heterozygous inactivation missense mutation led to hypoplastic dermal lymphatics and thickening of subcutaneous adipose tissue

Bano et al.: pituitary transcription factor-1 (Pit-1) mutation associated with lipedema over 4 generations

González-Parra et al.: changes of circulating sex steroids altered the regulation of Pit-1

Is lipedema a genetic condition?


CEBPD↓: transcription factor, involved in inflammatory responses, estrogen-regulated

KLF4↓: development of skin barrier, regulation of lipid metabolism/adipogenesis, macrophage polarization

CCDN1↑: early cancer onset, tumor progression, anchorage-independent growth, angiogenesis via VEGF production
Is lipedema a genetic condition?

Most genes carrying deleterious variants involved in steroidogenesis, lipid homeostasis, and insulin signaling.

**PLIN1**
perilipin-1, covers lipid storage droplets in adipocytes until broken down by hormone-sensitive lipases

**LIPE**
lipase E, hormone-sensitive, converts cholesteryl esters to free cholesterol for steroid hormone production.

**PPARG**
Peroxisome Proliferator Activated Receptor Gamma key regulator of adipocyte differentiation, glucose homeostasis, controls fatty acid beta-oxidation in peroxisomes

**NPC1**
Niemann-Pick disease, type C1, expressed in human white adipose tissue adipocytes, involved in obesity

**RYR1**
ryanodine receptor 1, calcium channel mediating the release of Ca2+ from SR into cytoplasm, triggers muscle contraction, normal embryonic development of skeletal muscle, heart, skin, and bones, involved in fat accumulation and distribution

**POMC**
preproopiomelanocortin, POMC-producing hypothalamic neurons regulate body weight, may serve as a critical node bridging poor early-life nutritional conditions to adult-life obesity and metabolic disorders

**NR0B2**
nuclear receptor subfamily 0, group B, member 2, orphan receptor, associated with subcutaneous fat tissue accumulation in mildly obese individuals

**GCKR**
glucokinase regulator, regulatory protein inhibiting glucokinase in liver and pancreatic islet cells, associated with fatty liver

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Is lipedema related to hormonal abnormalities?

- arcuate nucleus, POMC neurons: altered ER pattern
- basal lipolysis ↓ less in the abdominal than in the femoral region (also mediated by SNS)
- altered...
  - expression of lipogenic enzymes
  - lipoprotein lipase, lipin1 mRNA expression
  - ERα,β pattern/signaling pathway in the lipedematous tissue
- central effects
  - appetite
  - weight control
- peripheral effects
  - postmenopause: dysfunction of “switching” from gynoid to android adiposity

Is lipedema an inflammatory condition?

Immune cell infiltrate with increased macrophage presence in lipedema.

Increase in macrophage infiltration without affecting the T cell compartment.
(The evaluation of the macrophage polarization using CD80 (M1), iNOS (M1), CD163 (M2) and TGFβ (M2) as markers indicates an M2 phenotype)
Is lipedema an inflammatory condition?

Comparable lipid composition (L vs. C) in Tissue and Serum

Serum measurements
IFN-β, IFN-γ, IL 2, 8, 10, 12(p40), 12(p70), 19, 26, 27(p28), 32, 35 (IL-2, IL-8, IL-10, IL-12(p40), IL-12(p70), IL-19, IL-26, IL-27(p28), IL-32, IL-35), TNF superfamily 14 (TNFSF14), MMP-1, MMP-3.

Is lipedema a vasculopathic/lymphangiopathic condition?

No morphological changes of lymphatic vessels in lipedema. (PDPN/podoplanin, LYVE-1, PROX-1)

No morphological changes of blood vessels in lipedema.

Despite increased VEGF-C serum levels

Counterbalancing increased VEGFR2-expression by reduced Tie2-expression?

Is lipedema a vasculopathic/lymphangiopathic condition?

Healthy women  Lymphedema  Lipedema

With kind approval from Dr. René Hägerling, Charité, Berlin
Is lipedema associated with neuropathies?

Summary and Outlook: Lipedema...

... affects predominantly women, mostly after profound changes in hormonal status

... puts a huge disease burden on affected patients

... is associated with bilateral, symmetrical fat deposits developing downward from the hips, affected subcutaneous regions are tender and painful

... is difficult to diagnose clinically (due to its many faces)

... is not strictly associated with peripheral lymphedema

... does not appear to affect the lymphatic vasculature to a measurable extent,

but is a complex syndrome including genetic, inflammatory, hormonal, neuropathic and psychosomatic dimensions,

and we urgently need further research
Bedankt voor uw aandacht !

Merci beaucoup de votre attention !

Merci fir är Opmierksamkeet !

Question, comments ?

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