Lipedema and inflammation

Győző Szolnoky

CIRC annual meeting, Bologna (ITA)

Oct 25-26, 2019
Conflict of Interest

• Travel expenses (flight and accommodation) have been fully covered by CIRC
Hallmarks of lipedema

- **Cuffing sign**
- **Bilateral fat pads**
- **Retromalleolar fat pads**
General clinical features of lipedema

#1 Low risk of diabetes despite higher body mass index (BMI)
#2 Normal blood pressure despite obese BMI
#3 Gynoid shape and relatively low risk of cardiovascular morbidity
#4 Relative resistance of lipedematous fat loss to lifestyle changes
#5 Relatively normal lipid panel
#6 Soft skin
#7 Lower resting energy expenditure
#8 Hypermobility and gait abnormality
#9 Pain and easy bruising

Sanchez-de la Torre Y et al. Horm Mol Biol Clin Invest 2019
Inflammation in lipedema

Lymphatic insufficiency? Micro- and macrovascular changes?

Adipogenic inflammation?

Inflammatory cells and their cytokines?
MRI lymphography in lipedema

Lymph flow alterations in lipedema

<table>
<thead>
<tr>
<th>Tabla 4. Alteraciones linfogammagráficas.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacientes</td>
<td>83</td>
</tr>
<tr>
<td>Pacientes con algún grado de afectación</td>
<td>39 (47%)</td>
</tr>
<tr>
<td>Grado de alteración:</td>
<td></td>
</tr>
<tr>
<td>1- Bajo</td>
<td>14 (35,9%)</td>
</tr>
<tr>
<td>2- Bajo-moderado</td>
<td>19 (48,7%)</td>
</tr>
<tr>
<td>3- Moderado</td>
<td>6 (15,4%)</td>
</tr>
<tr>
<td>4- Moderado-severo</td>
<td>0%</td>
</tr>
<tr>
<td>5- Severo</td>
<td>0%</td>
</tr>
</tbody>
</table>

Forner-Cordero I et al. Rev Esp Med Nucl Imag Mol 2018
Figuras 1a y 1b. Lipedema estadio 3 con linfogammagrafía normal.

Figuras 2a y 2b. Lipedema estadio 1 con alteraciones linfogammagráficas grado bajo-moderado.

Figuras 3a y 3b. Lipedema estadio 2 con alteraciones linfogammagráficas bajo-moderado

Figuras 4a y 4b. Hallazgos moderados en niña de 18 años con lipedema estadio 2.
LIPEDEMA IS ASSOCIATED WITH INCREASED AORTIC STIFFNESS

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![Aortic stiffness index graph]

<table>
<thead>
<tr>
<th>Aortic stiffness index</th>
<th>Control</th>
<th>Lipoedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of values</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Minimum</td>
<td>1.574</td>
<td>3.000</td>
</tr>
<tr>
<td>25% Percentile</td>
<td>2.879</td>
<td>5.100</td>
</tr>
<tr>
<td>Median</td>
<td>3.699</td>
<td>6.050</td>
</tr>
<tr>
<td>75% Percentile</td>
<td>4.735</td>
<td>7.900</td>
</tr>
<tr>
<td>Maximum</td>
<td>6.542</td>
<td>9.100</td>
</tr>
<tr>
<td>Mean</td>
<td>3.761</td>
<td>6.242</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>1.216</td>
<td>1.842</td>
</tr>
<tr>
<td>Std. Error</td>
<td>0.3249</td>
<td>0.5318</td>
</tr>
</tbody>
</table>
Histological findings in lipedema: capillaries

Al-Ghadban S et al, J Obes 2019
Histological findings in lipedema: lymphatic vessels

Al-Ghadban S et al, J Obes 2019
Local pathognomonic features

- Capillary constriction in obese lipedema patients
- Increased capillary leakage and increased amount of interstitial fluid
- Hypoxia leads to adipocyte cell death and macrophage recruitment
- Lymph stagnation and concomitant inflammation stimulate adipogenesis and fibrosis

Al-Ghadban S et al, J Obes 2019
Indirect proofs of inflammation related to lymphatic insufficiency
Inflammation in lymphedema

Inflammation in lymphedema

Comparative microarray results:

- Lymphangiogenesis (FGFb)
- Inflammation (IL-4, IL-10, TNF beta)
- Fibrosis (TGFβ)

Rockson S. Lymphat Res Biol 2012
Role of Leukotriene B$_4$ in lymphedema

- Lymphangiogenesis
- Inflammation (eg. macrophage, PMNL and T lymphocyte recruitment; Th$_{17}$ differentiation)
- Fibroblast and adipocyte stimulation
- Edema formation

Jiang X et al. Annu Rev Physiol 2018
Inflammation in lymphedema: proposed pathophysiology of secondary lymphedema

Kataru RP et al. Front Immunol 2019
Adipogenic inflammation
Adipogenesis

Ghaben AL, Scherer PE. Nature Reviews 2019
Histological findings in lipedema: sizes of adipocytes

Al-Ghadban S et al, J Obes 2019
Lipedema vs Control: adipokine expression

Bauer AT et al, Plast Reconstr Surg 2019
Stromal vascular cells of lipedema

Priglinger E et al. Cytotherapy 2017
Inflammatory cells and their cytokines in lipedema
Lipedema vs Control: IGF-1 and IL-8 protein expressions

Bauer AT et al, Plast Reconstr Surg 2019
Histological findings in lipedema: macrophages

Al-Ghadban S et al, J Obes 2019
Grazie mille per l’attenzione!
Breast cancer treatment-related secondary lymphedema-associated genetic predispositions

Miaskowski C et al. PLOS One 2013
Breast cancer treatment-related secondary lymphedema-associated genetic predisposition

Inflammation in lymphedema

Table 1: Top 10 of the highest priority genes according to the criterion 6 calculated as the average value of five criteria.

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Protein name</th>
<th>Gene Id</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 A</th>
<th>4 B</th>
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<tbody>
<tr>
<td>KDR</td>
<td>Vascular Endothelial Growth Factor Receptor 2</td>
<td>3791</td>
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<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
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<td>1</td>
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<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor alpha</td>
<td>7124</td>
<td>20</td>
<td>7</td>
<td>32</td>
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<tr>
<td>TEK</td>
<td>TEK Receptor Tyrosine Kinase</td>
<td>7010</td>
<td>2</td>
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<td>19.5</td>
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<tr>
<td>BMPR2</td>
<td>Bone Morphogenetic Protein Receptor Type 2</td>
<td>659</td>
<td>15</td>
<td>12</td>
<td>25</td>
<td>9</td>
<td>10</td>
<td>18.5</td>
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<tr>
<td>SERPINE1</td>
<td>Serpin Family E Member 1</td>
<td>5054</td>
<td>10</td>
<td>27</td>
<td>36.5</td>
<td>9</td>
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<tr>
<td>IL10</td>
<td>Interleukin 10</td>
<td>3586</td>
<td>19</td>
<td>26</td>
<td>44</td>
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<tr>
<td>CD40LG</td>
<td>CD40 Ligand</td>
<td>959</td>
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<td>7</td>
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<tr>
<td>CCL2</td>
<td>C-C Motif Chemokine Ligand 2</td>
<td>6347</td>
<td>6</td>
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<tr>
<td>FASLG</td>
<td>Fas Ligand</td>
<td>356</td>
<td>7</td>
<td>9</td>
<td>40</td>
<td>19.5</td>
<td>27.5</td>
<td>11</td>
<td>9</td>
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<tr>
<td>ABL1</td>
<td>ABL Proto-Oncogene 1, Non-Receptor Tyrosine Kinase</td>
<td>25</td>
<td>4</td>
<td>4</td>
<td>42</td>
<td>9</td>
<td>7.5</td>
<td>49</td>
<td>10</td>
</tr>
</tbody>
</table>

*Control gene with known associations with lymphedema

Saik AV et al. BMC Med Genomics 2019