Obesity Paradox in Sepsis

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Disclosure / Conflict of Interest

• No Conflict of Interest with respect to this presentation.
Obesity Paradox

• Critically ill obese patients have better outcomes despite:
  – Diabetes
  – Respiratory dysfunction
  – Chronic inflammatory state

• Is this true in sepsis?
• Is the inflammatory response different?
• Relationship to cytokines, lipoprotein levels?
Critically ill obese patients: meta-analysis

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Obese (n/N)</th>
<th>Nonobese (n/N)</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marik P</td>
<td>1724/12011</td>
<td>6509/36165</td>
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<td>El-Solih A</td>
<td>35/117</td>
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<td>Garrouste-Orgemas M</td>
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<td>475/1471</td>
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<td>O'Brien JM</td>
<td>137/457</td>
<td>413/1031</td>
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<td>Ray D E</td>
<td>57/550</td>
<td>237/1598</td>
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<td>Aldawood</td>
<td>134/540</td>
<td>394/1295</td>
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<td>Bochicchio G</td>
<td>13/62</td>
<td>166/1105</td>
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<td>Nasraway S</td>
<td>22/366</td>
<td>87/1007</td>
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<td>Peake SL</td>
<td>26/129</td>
<td>69/304</td>
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</tr>
</tbody>
</table>

Total (95% CI): 14459/44108

Total events: 2205 (obese), 8372 (Nonobese)

Test for heterogeneity: $\chi^2 = 18.35$, df = 8 (P = 0.02), I² = 56.4%

Test for overall effect: $Z = 3.33$ (P = 0.0009)
60-Day In-Hospital Mortality
(ICON ICU patients n=8829)

Sakr et al. Crit Care Med. 2015
Septic shock: VASST

- ↑ creatinine 191 vs 130 μmol/L
- ↑ female 45 vs 38%
- ↓ fluid/kg 130 vs 180 mL/kg
- ↓ pressor/kg NE 0.13 vs 0.26
- ↓ pneumonia 35 vs 50%
- ↓ fungal 8.2 vs 15.6%

**BMI**
- BMI ≥30 kg/m² (obese)
- BMI 25-29.9 kg/m² (overweight)
- BMI <25 kg/m²

**Number at Risk**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>245 201 187 179 174</td>
</tr>
<tr>
<td>BMI 25-29.9 kg/m²</td>
<td>209 181 160 143 135</td>
</tr>
<tr>
<td>BMI &lt;25 kg/m²</td>
<td>276 220 183 169 162</td>
</tr>
</tbody>
</table>
LPS is sequestered in adipose tissue via VLDLR

**Decreased VLDLR expression using Vldlr knockout**

**A**

**Visceral adipose tissue**

![Graph showing LPS uptake in WT vs Vldlr -/-](image)

**B**

**Subcutaneous adipose tissue**

![Graph showing LPS uptake in WT vs Vldlr -/-](image)

**Increased VLDLR expression using Pcsk9 knockout**

**C**

**Visceral adipose tissue**

![Graph showing LPS uptake in WT vs Pcsk9 -/-](image)

**D**

**Subcutaneous adipose tissue**

![Graph showing LPS uptake in WT vs Pcsk9 -/-](image)
↑ VLDLR increases septic shock survival
(VLDLR rs7852409 C allele is gain-of-function)

Survival

Days

GG (n=305)  
CG (n=171)  
CC (n=43)
Cytokine inflammatory response
Subcutaneous adipose tissue may be “good” fat
Visceral adipose tissue may be “bad” fat

VAT/SAT
Visceral Adipose Tissue / Subcutaneous Adipose Tissue

High VAT/SAT (Bad?)

Low VAT/SAT (Good?)
High VAT/SAT is bad

P<0.005

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Days after enrollment</th>
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<tbody>
<tr>
<td>Quartile 1</td>
<td>64 61 57 56 54 53 52 51 50 50</td>
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<td>Quartile 2</td>
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<td>Quartile 3</td>
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</tr>
<tr>
<td>Quartile 4</td>
<td>64 56 41 39 34 34 34 31 31 31</td>
</tr>
</tbody>
</table>

90-day mortality by VAT/SAT

P=0.004

P=0.023

Pro/anti-inflammatory ratio: IL8 / IL10

VAT/SAT related to LDL, HDL?

![Survival](image1.png)

Low VAT/SAT vs High VAT/SAT on survival days.

![LDL](image2.png)

Box plots showing LDL levels for Low VAT/SAT vs High VAT/SAT.

P = 0.043 (difference in survival days)

P = 0.006 (difference in LDL levels)
Low LDL, HDL levels in sepsis

Low LDL, HDL are bad

VAT/SAT related to LDL, HDL?

Low VAT/SAT vs. High VAT/SAT

Survival

Days

P = 0.043

LDL

Low VAT/SAT vs. High VAT/SAT

P = 0.006
Conclusions

• Obesity paradox is particularly strong in sepsis
  – High BMI protects against mortality
  – Better nutritional state?
  – Sequesters pathogen lipids?
• Low VAT/SAT is beneficial at any BMI
• Subcutaneous Adipose Tissue (SAT) is good
  – Not as pro-inflammatory as VAT
  – Protects against lipoprotein drop
Clinical Implications

• Another reason nutrition is important?
• Novel strategies to increase LPS sequestration in adipose tissue (PCSK9 inhibitors)?
• Do anti-inflammatory therapies work better in patients with high VAT/SAT?
• Important to understand why low LDL, HDL are low in sepsis and associated with adverse outcome (supplement HDL?)
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Mihai Cirstea
Chawika Pisitsak
Bandarn Suetrong
Kelly Genga
Joseph Lee

VASST Investigators

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Size of the problem

Severe Sepsis
All hospitalized
Half ICU