The Obesity Paradox

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UBC patent application re: PCSK9 licensed to Cyon Therapeutics. Walley, Russell, Boyd are inventors and founders of Cyon.
Lipids / Adipose Tissue in Sepsis

- Obesity paradox? So something is up.
- Visceral vs subcutaneous adipose tissue
- Pathogen lipids carried in lipoproteins
- Effect of PCSK9 suggests that good liver function (LDLR) and lots of adipose tissue (VLDLR) may ↑ pathogen lipid clearance
Obesity Paradox
Critically ill patients meta-analysis

Review: Influence of obesity on mortality in intensive care units
Comparison: 01 RCT
Outcome: 01 In-hospital Mortality

<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>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
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<tbody>
<tr>
<td>Mark P</td>
<td>1724/12011</td>
<td>6509/36165</td>
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<td>El-Soh A</td>
<td>35/117</td>
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<td>24.78</td>
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<td>Garrouste-Orgas M</td>
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<td>475/1471</td>
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<td>O'Brien JM</td>
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<td>Ray DE</td>
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<td>10.20</td>
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<td>Aldawood</td>
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<td>Nasraway S</td>
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<td>87/1007</td>
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<td>[0.44, 1.09]</td>
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<td>Peake SL</td>
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<td>69/304</td>
<td>5.96</td>
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<td>[0.59, 1.33]</td>
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</tbody>
</table>

Total (95% CI)        | 14459        | 44108          | 100.00             | 0.83     | [0.74, 0.92]        |

Total events: 2205 (obese), 8372 (Nonobese)
Test for heterogeneity: $\chi^2 = 18.35$, df = 8 ($P = 0.02$), $I^2 = 56.4\%$
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

p = 0.018
Septic Shock: VASST

Wacharasint et al. Crit Care 17(3), R122, 2013

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

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<tr>
<th>Number at Risk</th>
<th>Days</th>
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<tr>
<td>BMI ≥30 kg/m²</td>
<td>245</td>
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<td>BMI 25-29.9 kg/m²</td>
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</table>
Cytokine Inflammatory Response

Wacharasint et al. Crit Care 17(3), R122, 2013
More than BMI?

Visceral Adipose Tissue / Subcutaneous Adipose Tissue (VAT/SAT)

VAT/SAT Quartiles

Cum Survival

P=0.028 at day 28

P=0.005 at day 90
VAT/SAT $\rightarrow$ Mortality

$\text{BMI} < 25 \text{ kg/m}^2$

$\text{BMI} \geq 25 \text{ kg/m}^2$

$p = 0.005$ (linear by linear association)
VAT may be “bad” fat

Could SAT be Good?
Are Plasma Lipids Also Involved In Sepsis?
Lipoproteins in Sepsis?
Central role for LDL and VLDL receptors

Pathogen lipid (e.g. LPS, LTA)

Pro-inflammatory response

TLR and other innate immune receptors

Macrophage/monocyte; other cell lines

Activation of inflammatory cytokines, upregulation of adhesion molecules, iNOS induction, etc.

Sequestration / Clearance

HDL

Transfer proteins (LBP, BPI, PLTP, CETP)

LDL

VLDL

LDLR

Hepatocyte
Elevated PCSK9 is Bad
PCSK9 reduces LDL and VLDL receptor numbers
Increased PCSK9 Function is Bad

VASTT

\[ p = 0.0054 \]

SPH

\[ p = 0.022 \]
PCSK9 May Decrease LPS Clearance Via LDLR (Liver) and VLDLR (Adipose Tissue)

- Lipopolysaccharide (LPS) Gram -
- Endotoxin
- Lipoteichoic acid (LTA) Gram +
The Obesity Paradox
(Lots of speculation here)

• Obesity paradox? So something is up.
• Visceral adipose tissue is bad and/or subcutaneous adipose tissue is good
• Pathogen lipids carried in lipoproteins
• Effect of PCSK9 suggests that good liver function (LDLR) and lots of adipose tissue (VLDLR) may ↑ pathogen lipid clearance
UBC co-investigators
John Boyd
Jim Russell
Gordon Francis

U Penn co-investigators
Muredach Reilly
Nuala Meyer
Jason Christie
Jane Ferguson

Databases
VASST Investigators

People
Chawika Pisitsak
Mihai Cirstea
Elena Topichy
Taka Nakada
Petch Wacharasint
Katherine Thain
Simone Thair
Lynda Lazosky

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CIHR
NIH

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