NASH: What’s Bile Got to Do With It?

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Disclosures
I have the following relationships to disclose:

– Ethicon Endo Surgery Inc.
– Galectin Pharmaceuticals
– Synageva Biopharma/Alexion
– Raptor Pharmaceuticals
– Lumena/Shire

I will be discussing off-label use of medications in my presentation

Weight Loss Interventions

• Lifestyle
• Drug therapy
• Bariatric surgery

Severe NASH now considered indication for surgery in adolescents

Selection criteria for adolescent weight loss surgery

<table>
<thead>
<tr>
<th>BMI</th>
<th>Comorbidities</th>
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<tbody>
<tr>
<td>&gt; 35</td>
<td>• Type 2 DM</td>
</tr>
<tr>
<td></td>
<td>• moderate-severe OSA (AHI ≥ 15 events/hr)</td>
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<tr>
<td></td>
<td>• pseudotumor cerebri</td>
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<tr>
<td></td>
<td>• severe NASH</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>• Mild OSA (AHI&gt;5 events/hr)</td>
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<tr>
<td></td>
<td>• HTN</td>
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<tr>
<td></td>
<td>• Insulin resistance/IGT</td>
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<td></td>
<td>• Dyslipidemia</td>
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<td></td>
<td>• impaired QOL or ADL</td>
</tr>
</tbody>
</table>

Pratt, JSA et al. Obesity 2009; 17:901

But how does this “Bariatric Surgery” WORK to improve NASH?

Potential Mechanisms behind Bariatric Procedures

• Obvious
  – Restriction
  – Malabsorption

• Not so obvious
  – Altered metabolic pathways/processes
    • Increased energy expenditure
    • Signaling for early satiation
Restriction?

Potential Mechanisms behind Bariatric Procedures

• Obvious
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Background: Bariatric Surgery Increases Fasting Serum Bile Acids

Body mass index is decreasing and, on the contrary, fasting total serum bile acid levels are increasing after bariatric surgery.

Metabolism 58(10):1400-7 (2009)
Effect of Bariatric Surgery on Serum Bile Acid Levels


Verticoal Sleeve Gastrectomy

Roux-en-Y Gastric Bypass

Gastric Banding


How can we study this BA phenomenon in Bariatric Surgery?

Normal Enterohepatic Circulation

Liver

Dietary Cholesterol

Duodenum

Jejunum

Ileum

Excretion

Plasma

Key

Cholesterol

Bile Acids
**Results: Change in Body Weight**


* = p<0.05

**Results: Serum Bile Acids**


*** = p<0.001

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**Altered Enterohepatic Circulation**

Liver

Dietary Cholesterol

Cholesterol

Bile Acids?

Duodenum

Transposed ileum

Jejunum

Plasma

Excrètion

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Bile diversion

Body Weights

Kohli et al., Endocrinology, 2013 Apr 16.
**Bile Diversion**
Fasting serum bile acid

![Graph showing bile acid levels in Sham and BD conditions](image)

Kohli et al., Endocrinology, 2013 Apr 16.

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**IT and BD Study - Conclusions**

- IT and BD surgery in rat models
  - Reproduces the metabolic benefits of bariatric surgery
  - Loss of fat mass
  - Improvement in insulin sensitivity
  - Increases GLP-1 and Serum Bile Acids

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**Do these procedures impact bile acid composition?**

**Altered Enterohepatic Circulation**

- Dietary Cholesterol
- Cholesterol
- Bile Acids
- Plasma
- Liver
- Duodenum
- Transposed ileum
- Jejunum
- Excretion

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**Bile Acid Conjugation**

- Final Step in Bile Acid Synthesis
- Rate-limiting Step

**Bile acid-CoA ligase (BACL)**
- Gene: SLC27A5 (19q13.43)

**Bile acid-CoA: Amino Acid N-acyl Transferase (BAAT)**
- Gene: BAAT (9q22.3)

- Cholic acid
- Cholic acid-CoA
- Conjugated Cholate
- Secreted in Bile

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**Area Under the Curve**

- AUC [μmol·min⁻¹·L⁻¹]
- Total
- Conj
- Quer
- Unconj

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Results: Serum Bile Acids

Serum Conjugated Bile Acids (ng/mL)

Bile Diversion

Kohli et al., Endocrinology, 2013 Apr 16.

So what about the "established" bariatric procedures?

Vertical Sleeve Gastrectomy

Modified from Myronovych, Kohli et al Obesity 2014; 22 (2) 390-400.

Body Weight Change after VSG

Modified from Myronovych, Kohli et al Obesity 2014; 22 (2) 390-400.
Serum Bile Acid Levels after VSG

Fasting Bile Acids

14 Days Post Surgery

Myronovych, Kohli et al. Obesity 2014; 22 (2) 390-400.

After VSG
TUDCA is higher again!

Myronovych, Kohli et al. Obesity 2014; 22 (2) 390-400.

So why not just give TUDCA or GUDCA?
Bile Acid Diarrhea!
Bile Acid-FXR Pathway


FXR is a molecular target for the effects of vertical sleeve gastrectomy


Fxr ko mice can eat through a smaller stomach!

So is that it?

Is FXR the answer?

NASH Therapeutics

Lifestyle  Rx/Sx  Lifestyle

Articles

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

Obeticholic acid (OCA) improved the histological features of NASH in adults

but

Decreased HDL
Increased LDL
NO Pediatric Data on OCA in NASH
Uhhh... not so fast...

Microbiome has an influence

Bile Acid-FXR-SHP Pathway


VSG Works in SHP KO Mice

Body Weight Change

0 7 14 21 28 35 42 49 56 60

WT Sham
WT VSG
SHP KO Sham
SHP KO VSG

*=P<0.05
**=P<0.01
***=P<0.001

Bile Acids are Elevated VSG in SHP KO mice

4 Weeks Fasting Bile Acids

WT Sham
WT VSG
SHP KO Sham
SHP KO VSG

*=P<0.05
**=P<0.01
***=P<0.001

Unanswered questions
Questions?