NASH IMPROVEMENT AFTER BARIATRIC SURGERY: THE ROLE OF BILE ACID SIGNALING

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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
Pediatric NASH is real!

The Big Question:
What are the treatment options for NASH?

NASH Therapeutics
Lifestyle
Lifestyle
What if all this does not work?

NASH Therapeutics

Lifestyle • Rx/Sx • Lifestyle

Weight Loss Interventions

• Lifestyle
• Drug therapy
• Bariatric surgery

Severe NASH now considered indication for surgery in adolescents

<table>
<thead>
<tr>
<th>Selection criteria for adolescent weight loss surgery</th>
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<tr>
<td><strong>BMI</strong></td>
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<td>&gt; 35</td>
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Pratt JS et al. Obesity 2009; 17:901

Common Bariatric Surgery Procedures

Gastric Bypass  Gastric Banding  Sleeve Gastrectomy

Serum bile acid along with plasma incretins and serum high-molecular weight adiponectin levels are increased after bariatric surgery. (Hirushi Nakanuma, Kanetomi Kiyamu, Takeshi Ohinite, Mitsuhito Watanabe, Metabolism Clinical and Experimental 58(10): 1400-7 (2009))

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

How can we study this BA phenomenon in Bariatric Surgery?
Normal Enterohepatic Circulation

![Diagram of Normal Enterohepatic Circulation](image)

Altered Enterohepatic Circulation

![Diagram of Altered Enterohepatic Circulation](image)

Results: Change in Body Weight

![Graph showing change in body weight](image)
Results: Serum Bile Acids

![Graph showing fasting serum bile acid levels](image)


***=p<0.001

Bile Diversion

![Diagram of bile diversion](image)

Image Courtesy Jose Berger, MD
**Body Weights**

<table>
<thead>
<tr>
<th>Body Weight (g)</th>
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<tbody>
<tr>
<td>Naive</td>
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<tr>
<td>Sham</td>
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<tr>
<td>BD</td>
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**Fasting serum bile acid**

- **Sham**
- **BD**

**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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**Kohli et al., Endocrinology, 2013 Apr 16.**
Do these procedures impact bile acid composition?
Altered Enterohepatic Circulation

Results: Serum Bile Acids

Bile Diversion

So what about the "established" bariatric procedures?

Body Weight Change after VSG

Mironovych, Kohli et al Obesity (2014)
TUDCA is higher after VSG

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**


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**Fxr ko mice can eat through a smaller stomach!**


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**So is that it?**

**Is FXR the answer?**
Obeticholic acid (OCA) improved the histological features of NASH in adults

but

1. Safety of OCA use for NASH needs further clarification:
   • Decrease HDL
   • Increase LDL
2. No Pediatric Data on OCA in NASH
Unanswered questions

Questions?