

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



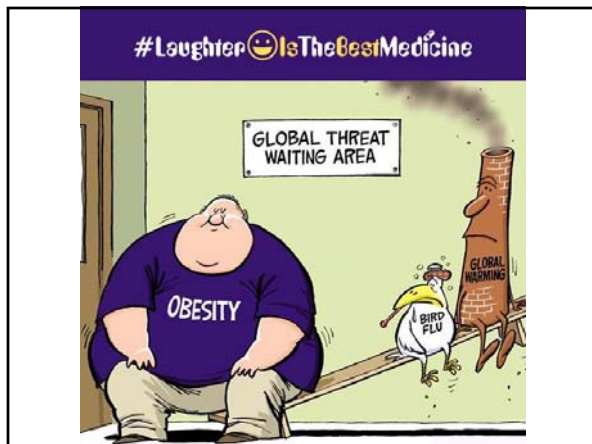
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Associate Professor of Pediatrics
Gastroenterology, Hepatology, & Nutrition

Disclosures

I have the following relationships to disclose:

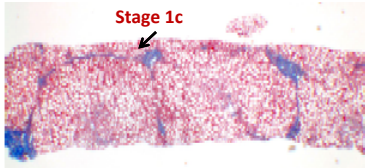
- Ethicon Endo Surgery Inc.
- Galectin Pharmaceuticals
- Synageva Biopharma/Alexion
- Raptor Pharmaceuticals
- Lumena/Shire

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



Pediatric NASH is real!

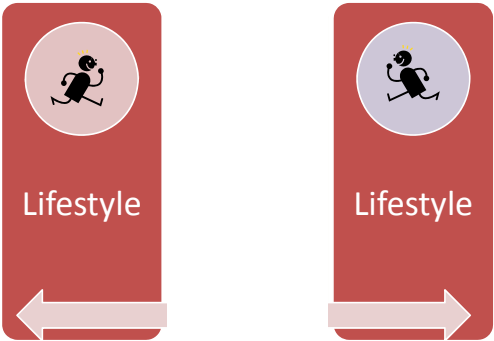
January
2009
Age 10



The Big Question:

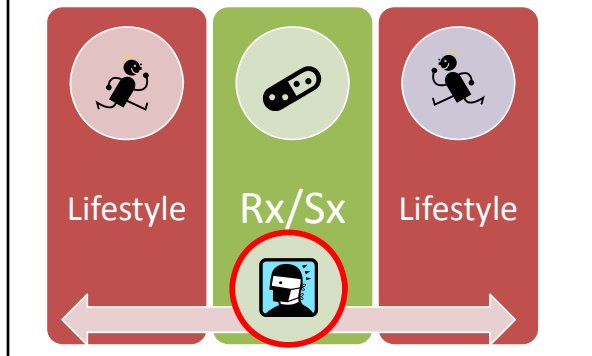
What are the treatment options for NASH?

NASH Therapeutics



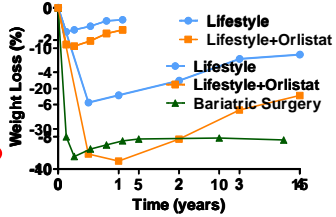
What if all this does not work?

NASH Therapeutics



Weight Loss Interventions

- Lifestyle
- Drug therapy
- **Bariatric surgery**



Annals of Surgery 222(3):339-50(1995)
Diabetes Care 27(1):155-61 (2004)

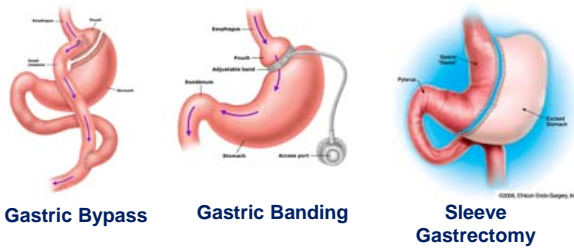
Severe NASH now considered indication for surgery in adolescents

Selection criteria for adolescent weight loss surgery

BMI	Comorbidities
> 35	<ul style="list-style-type: none"> Type 2 DM moderate-severe OSA (AHI \geq 15 events/hr) pseudotumor cerebri severe NASH
> 40	<ul style="list-style-type: none"> Mild OSA (AHI > 5 events/hr) HTN Insulin resistance/IGT Dyslipidemia impaired QOL or ADL

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

Common Bariatric Surgery Procedures



Gastric Bypass

Gastric Banding

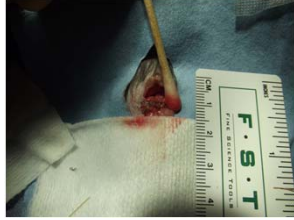
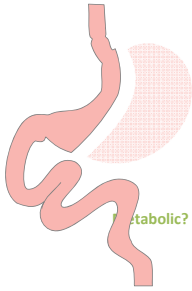
Sleeve Gastrectomy

The collage features several elements: a man in a suit on the left, a central photo of a man speaking, and two graphs. The top graph shows 'Fasting Total Serum Bile Acids (umol/L)' with bars for Gastric Bypass and Sleeve Gastrectomy. The bottom graph, labeled 'A', shows 'Fasting Total Serum Bile Acids (umol/L)' for three groups: LRYGB, LNU, and Health. A red box with white text is overlaid on the collage, stating: 'Weight Loss Induced by Sleeve Gastrectomy Not Laparoscopic Adjustable Gastric Banding Increases Circulating Bile Acids'. Citations at the bottom are: Kohli et al, J Clin Endocrinol Metab. 98(4):E708-12. (2013) and Steinart et al, Obesity. 21(12) E660-668. (2013).

Gastric Bypass

Sleeve Gastrectomy

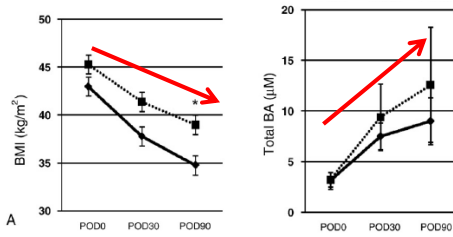
Vertical Sleeve Gastrectomy



Myronovych, Kohli et al Obesity (2014)

Serum bile acid along with plasma incretins and serum high-molecular weight adiponectin levels are increased after bariatric surgery

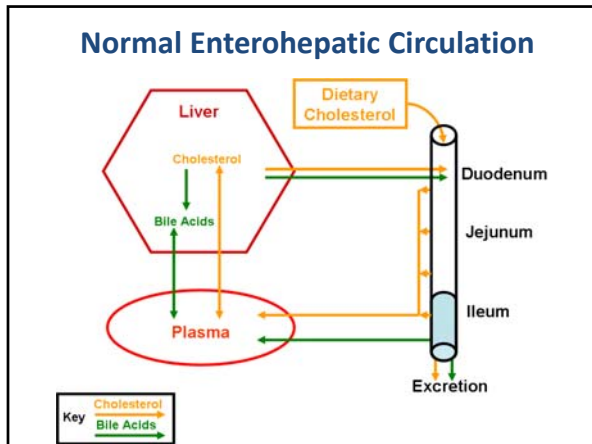
Hiroshi Nakatani^a, Kazunori Kasama^b, Takashi Oshiro^b, Mitsuhiro Watanabe^a,
Metabolism Clinical and Experimental 58 (2009) 1400–1407

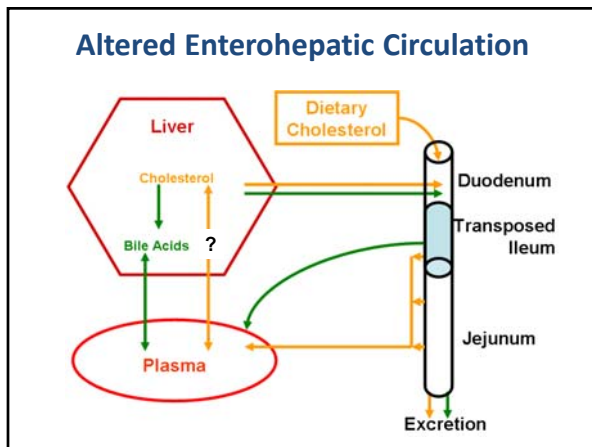


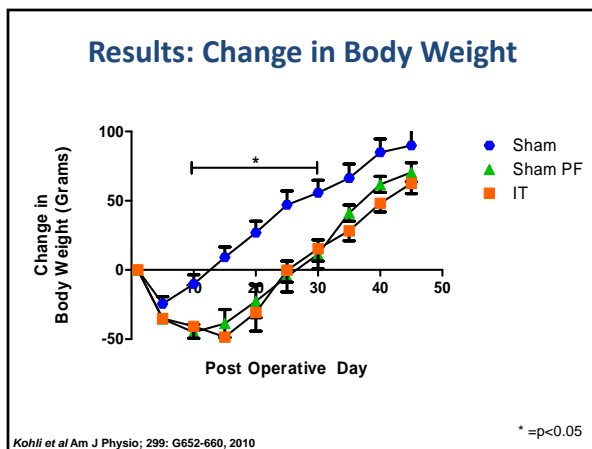
Body mass index is decreasing and, on the contrary, fasting total serum bile acid levels are increasing after bariatric surgery.

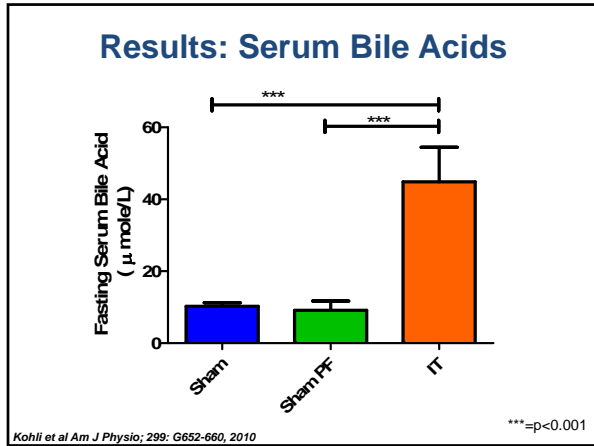
Metabolism 58(10):1400-7 (2009)

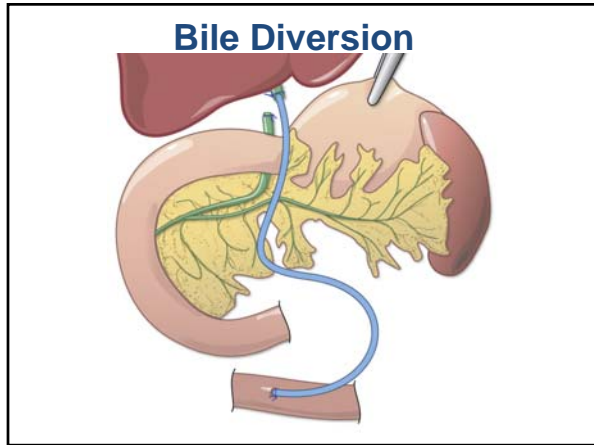
How can we study this BA phenomenon in Bariatric Surgery?

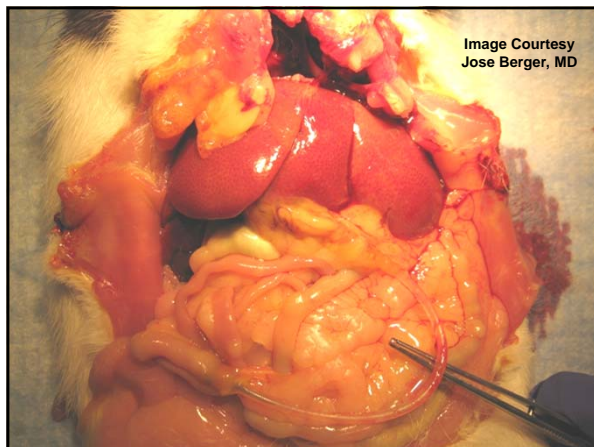


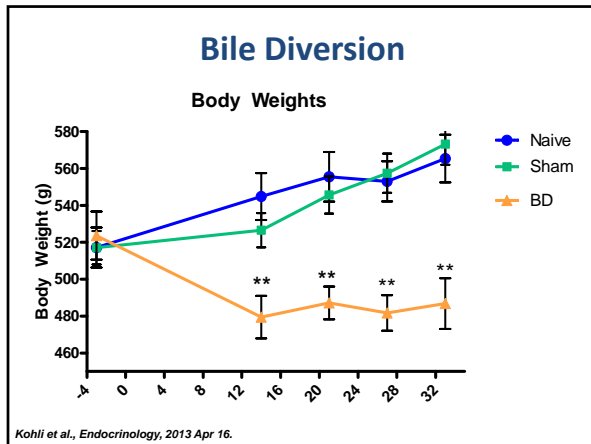


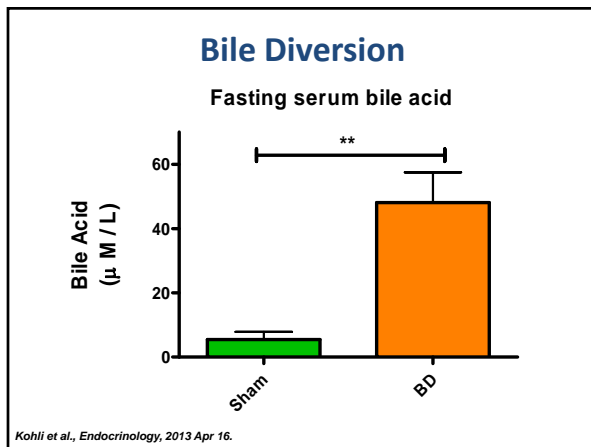








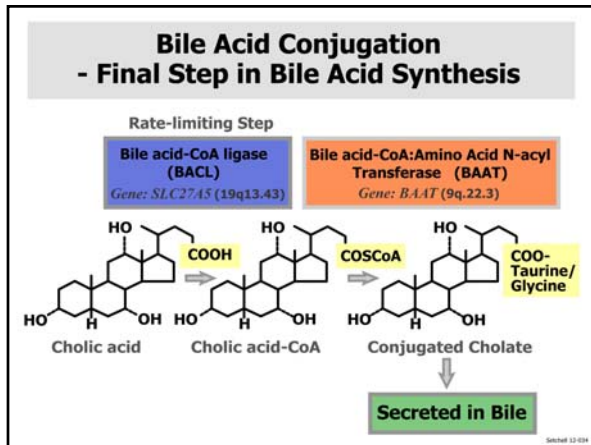


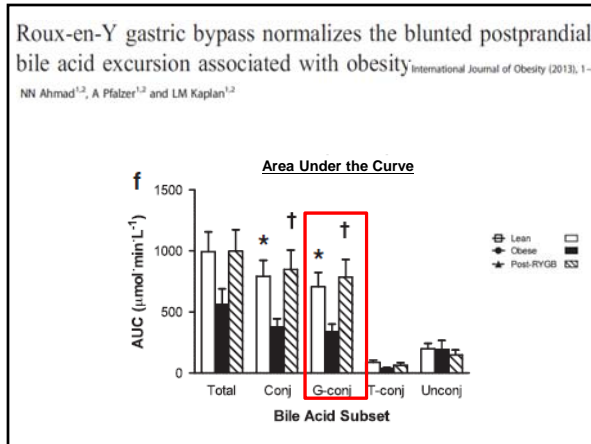


IT and BD Study - Conclusions

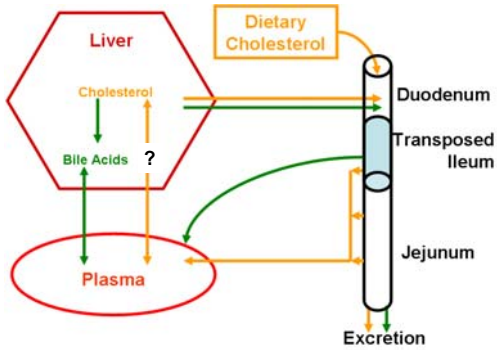
- **IT and BD surgery in rat models**
 - Reproduces the metabolic benefits of bariatric surgery
 - Loss of fat mass
 - Improvement in insulin sensitivity
 - Increases GLP-1 and **Serum Bile Acids**

Do these procedures impact bile acid composition?

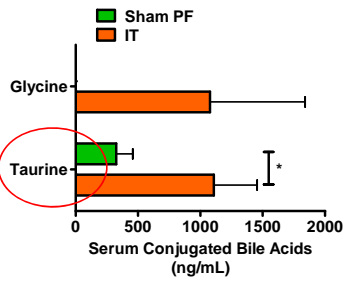




Altered Enterohepatic Circulation

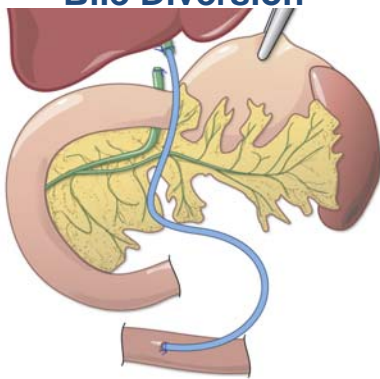


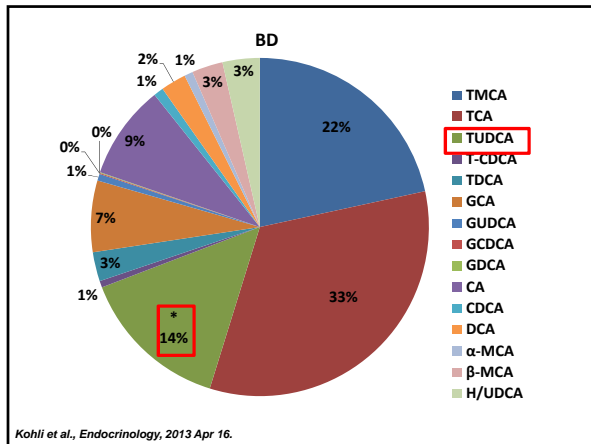
Results: Serum Bile Acids



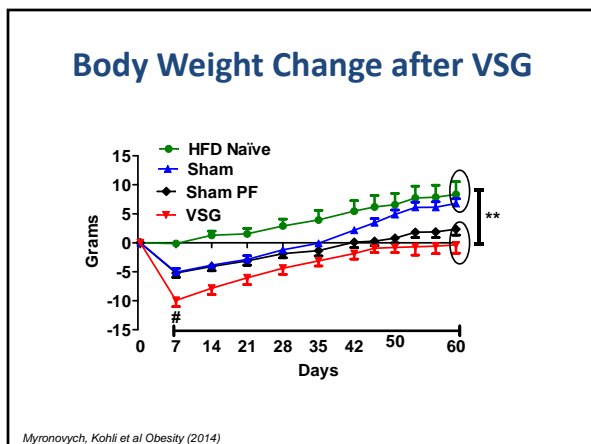
Kohli et al Am J Physiol; 299: G652-660, 2010

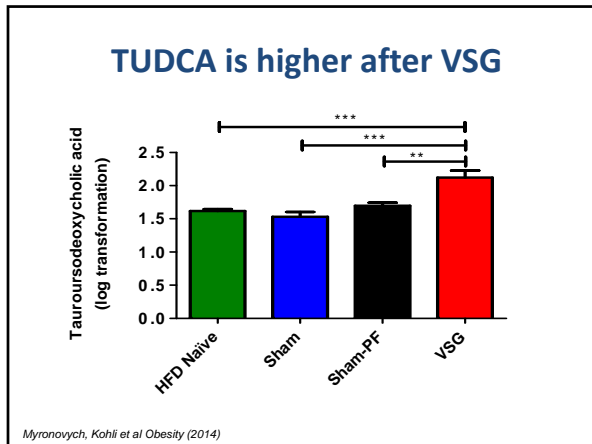
Bile Diversion





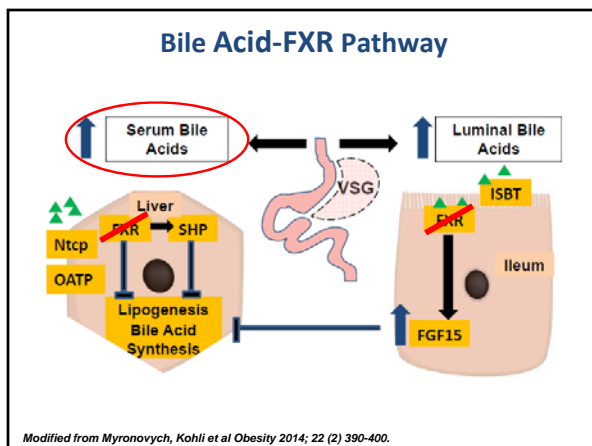
So what about the ***“established”*** bariatric procedures?





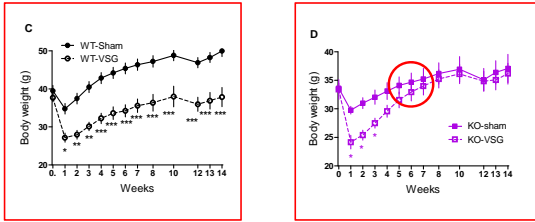
So why not just give TUDCA or GUDCA?

Bile Acid Diarrhea!



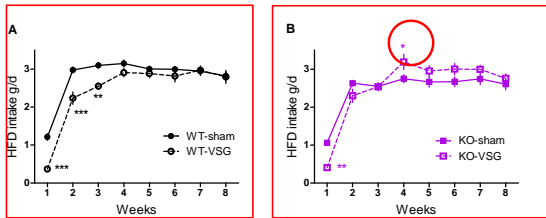
FXR is a molecular target for the effects of vertical sleeve gastrectomy

Karen E. Ryan¹, Valentina Tremaroli², Christoffer Clemmensen^{1,3}, Petia Kovatcheva-Datchary², Andriy Myronovych⁴, Rebekah Karns⁵, Hilary E. Wilson-Perez², Darleen A. Sandoval¹, **Bobbi Kohli¹**, Fredrik Backhed^{1,2} & **Randy J. Seeley¹**



Modified from Ryan, Kohli, Seeley et al Nature, May 8, 2014

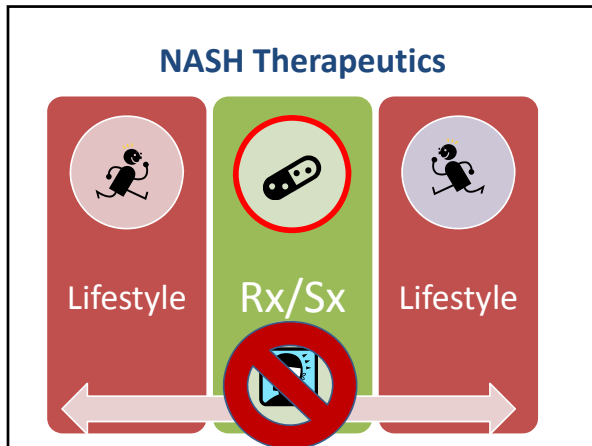
Fxr ko mice can eat through a smaller stomach!



Modified from Ryan, Kohli, Seeley et al Nature, May 8, 2014

So is that it?

Is FXR the answer?



Articles

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

Prof Brent A Neuschwander-Tetri, MCh, MCh, Rohit Loomba, MD, Prof Arun J Sanyal, MD, Prof Joel E Lavine, MD, Mark S Van Natta, MHS, Manal F Abdelmalek, MD, Prof Naga Chalasani, MD, Srinivasan Dasarthy, MD, Prof Anna Mae Diehl, MD, Bilal Hameed, MD, Prof Kish V Kowdley, MD, Prof Arthur McCullough, MD, Prof Norah Terrault, MD, Prof Jeanne M Clark, MD, Prof James Tonascia, PhD, Prof Elizabeth M Brun, MD, David F Kleiner, MD, Edward Des, MD, For the NASH Clinical Research Network¹

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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**

