

NASH :
What's Bile Got to Do With It?



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Gastroenterology, Hepatology, & Nutrition

Disclosures

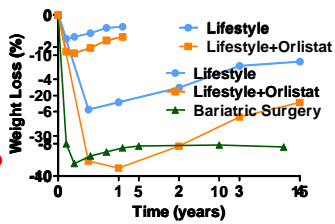
I have the following relationships to disclose:

- 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

Weight Loss Interventions

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



Annals of Surgery 222(3):339-501995 (1995)
Diabetes Care 27(1):155-61 (2004)

Severe NASH now considered indication for surgery in adolescents

Selection criteria for adolescent weight loss surgery

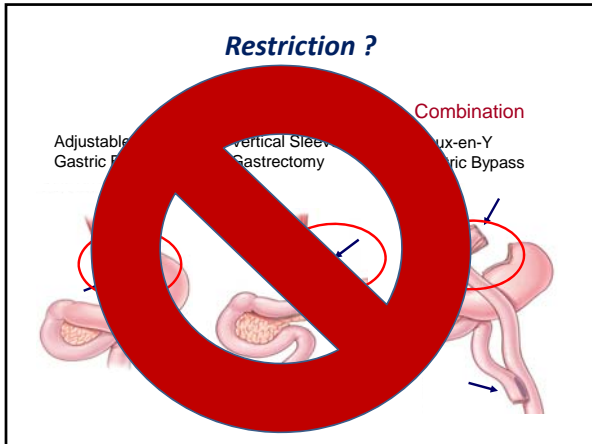
BMI	Comorbidities
> 35	<ul style="list-style-type: none">• Type 2 DM• moderate-severe OSA (AHI \geq 15 events/hr)• pseudotumor cerebri• severe NASH
> 40	<ul style="list-style-type: none">• Mild OSA (AHI > 5 events/hr)• HTN• Insulin resistance/IGT• Dyslipidemia• impaired QOL or ADL

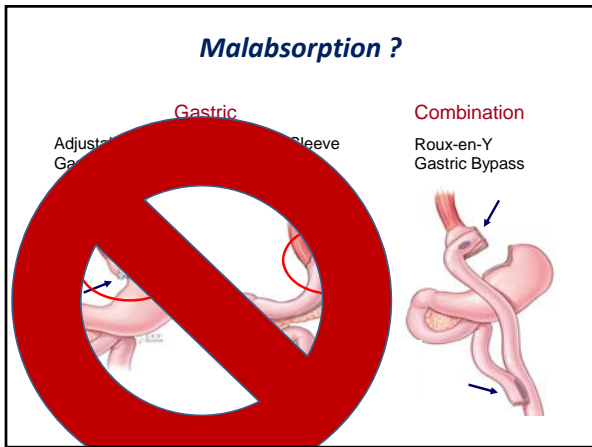
Pratt, JSA et al. Obesity 2009; 17:901

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

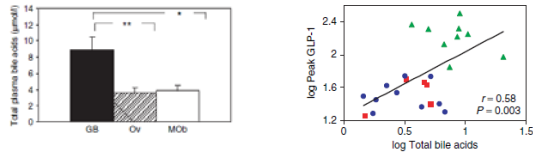




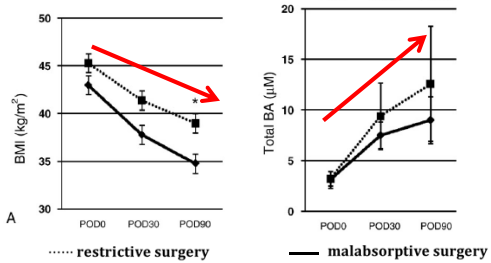
- Potential Mechanisms behind Bariatric Procedures**
- **Obvious**
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 - Signaling for early satiation

Serum Bile Acids Are Higher in Humans With Prior Gastric Bypass: Potential Contribution to Improved Glucose and Lipid Metabolism

Mary-Elizabeth Patti^{1,2}, Sander M. Houten¹, Antonio C. Bianco⁴, Raquel Bernier¹, P. Reed Larsen^{1,3}, Jens J. Holst⁶, Michael K. Badman^{1,7}, Eleftheria Maratos-Flier^{1,7}, Edward C. Mun^{1,3}, Jussi Pihlajamaki^{1,2}, Johan Auwerx⁸ and Allison B. Goldfine^{1,2,3} *OBESITY | VOLUME 17 NUMBER 9 | SEPTEMBER 2009*



Bile Acids and Bariatric Surgery

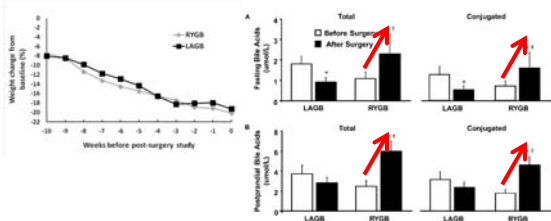


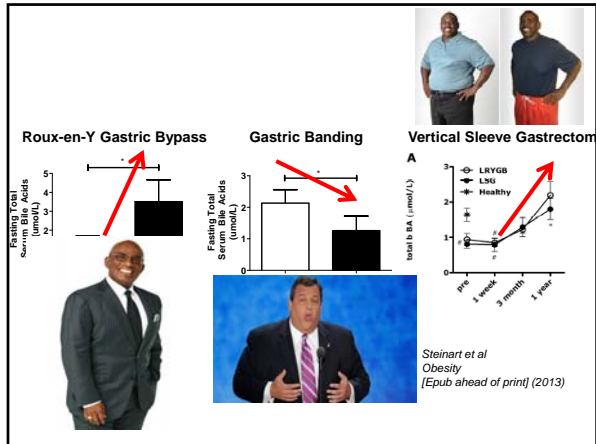
Body mass index is decreasing and, on the contrary, fasting total serum bile acid levels are increasing after bariatric surgery.

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

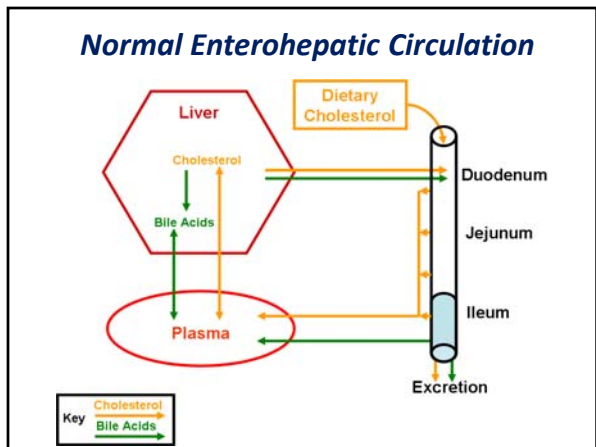
Weight Loss Induced by Roux-en-Y Gastric Bypass But Not Laparoscopic Adjustable Gastric Banding Increases Circulating Bile Acids

J Clin Endocrin Metab. First published ahead of print March 1, 2013
Rohit Kohli,* David Bradley,* Kenneth D. Setchell, J. Christopher Eagon, Nada Abumrad, and Samuel Klein

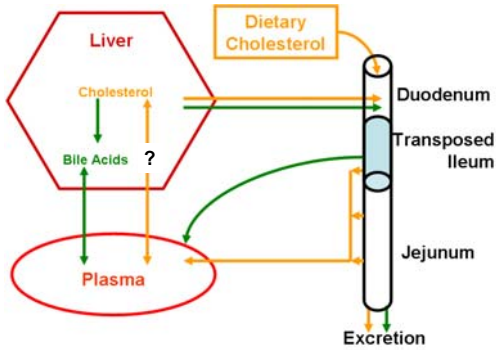




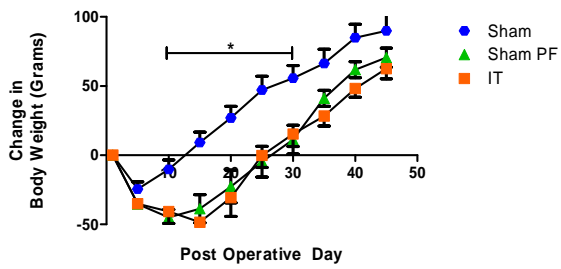
How can we *study* this BA phenomenon in Bariatric Surgery?



Altered Enterohepatic Circulation



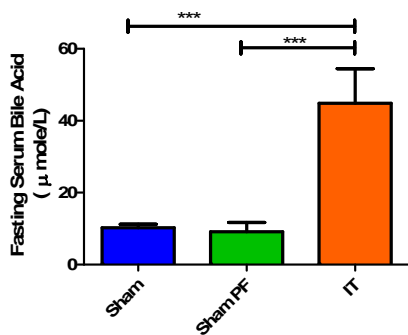
Results: Change in Body Weight



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

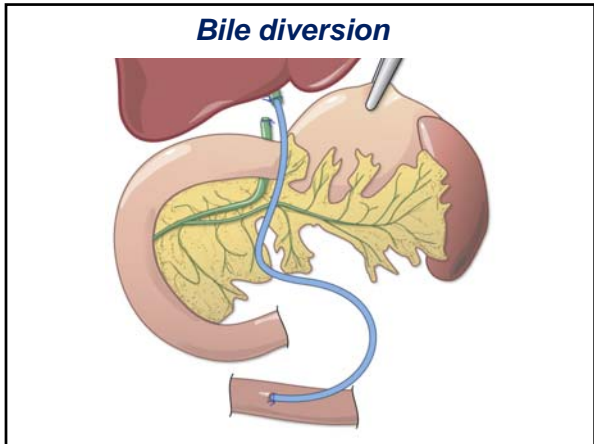
* =p<0.05

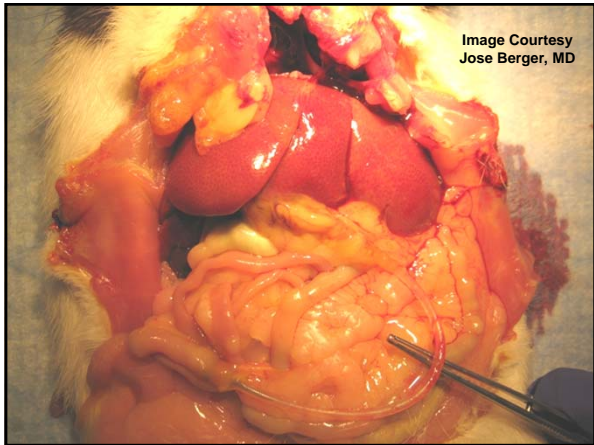
Results: Serum Bile Acids

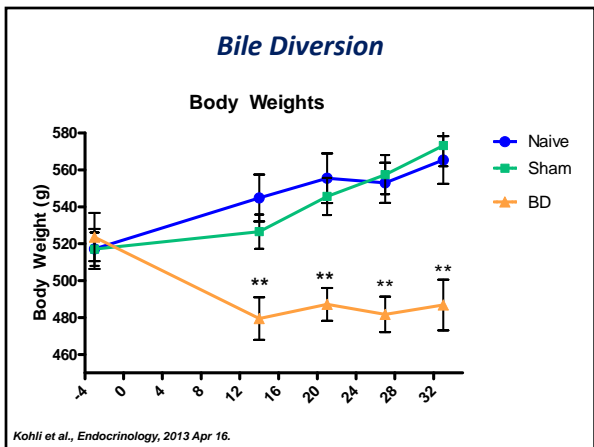


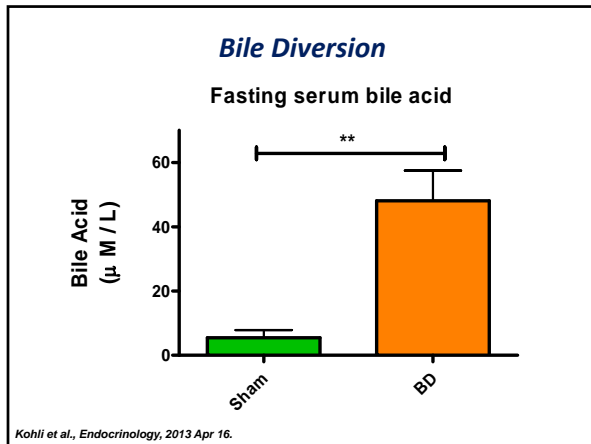
Kohli et al Am J Physiol; 299: G652-660, 2010

***=p<0.001



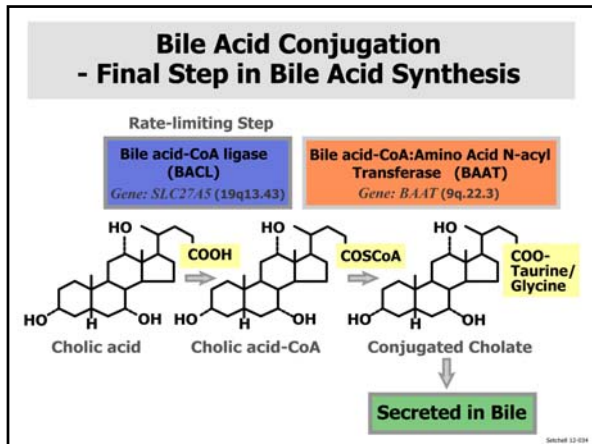


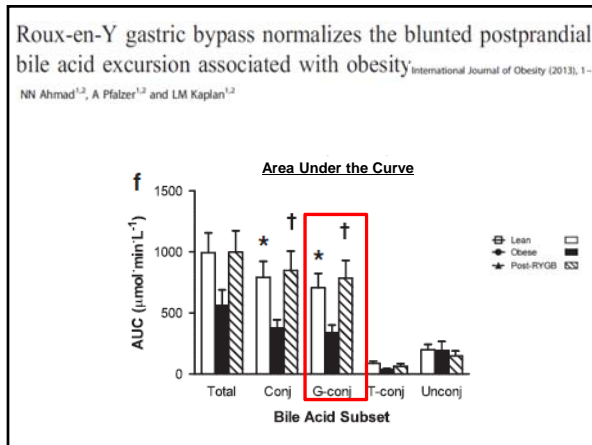


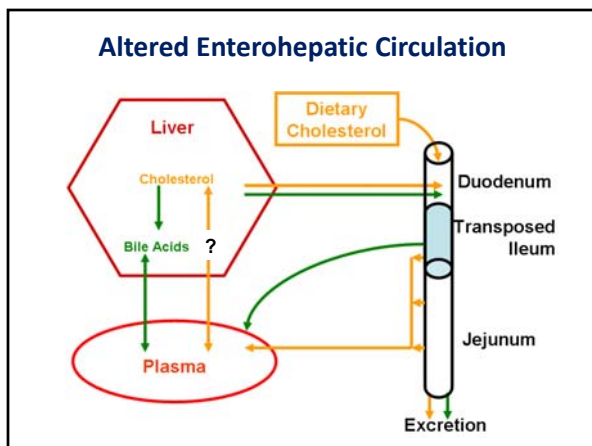


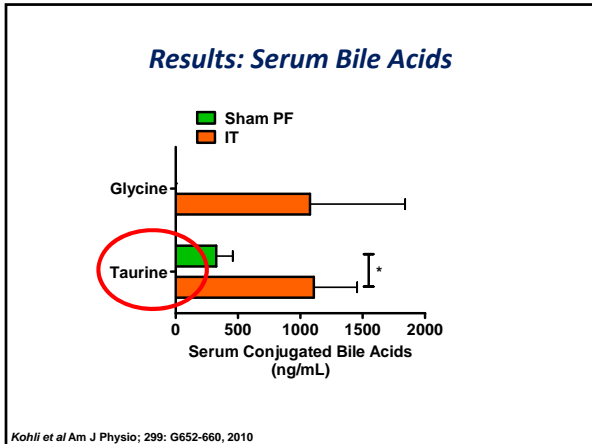
- IT and BD Study - Conclusions***
- **IT and BD surgery in rat models**
 - Reproduces the metabolic benefits of bariatric surgery
 - Loss of fat mass
 - Improvement in insulin sensitivity
 - **Increases** GLP-1 and **Serum Bile Acids**

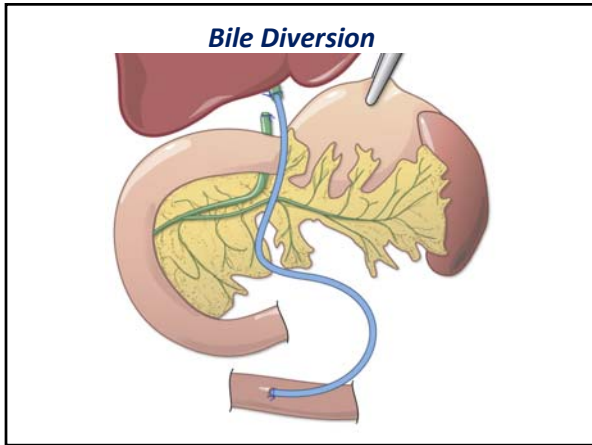
Do these procedures impact bile acid composition?

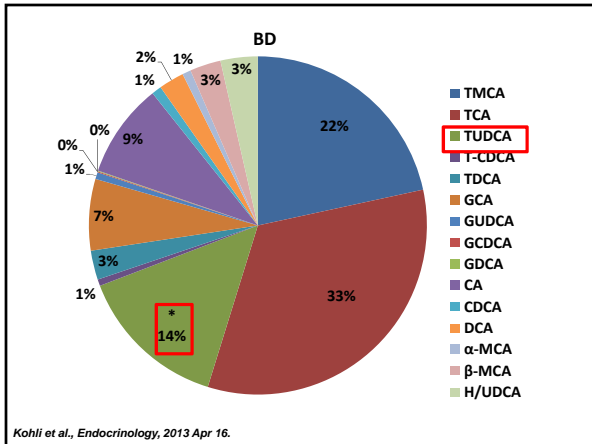






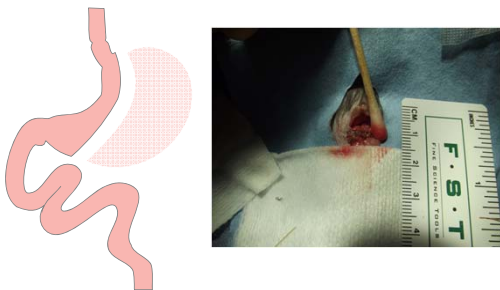






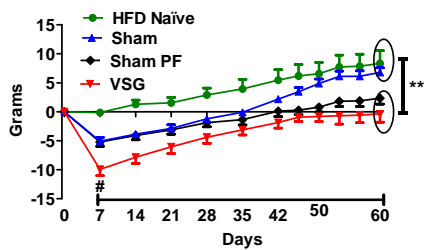
So what about the
“established”
 bariatric procedures?

Vertical Sleeve Gastrectomy



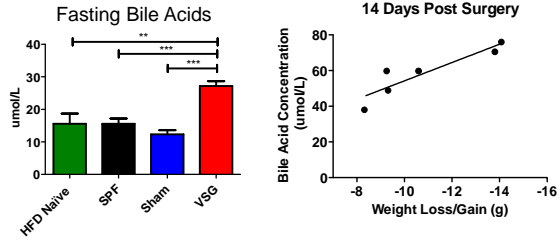
Modified from Myronovych, Kohli et al Obesity 2014; 22 (2) 390-400.

Body Weight Change after VSG



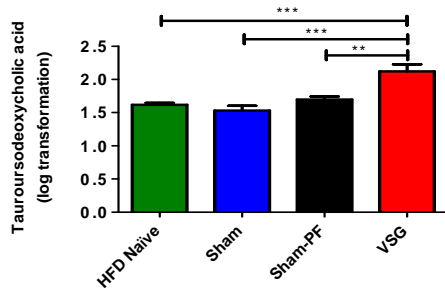
Myronovych, Kohli et al Obesity 2014; 22 (2) 390-400.

Serum Bile Acid Levels after VSG



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

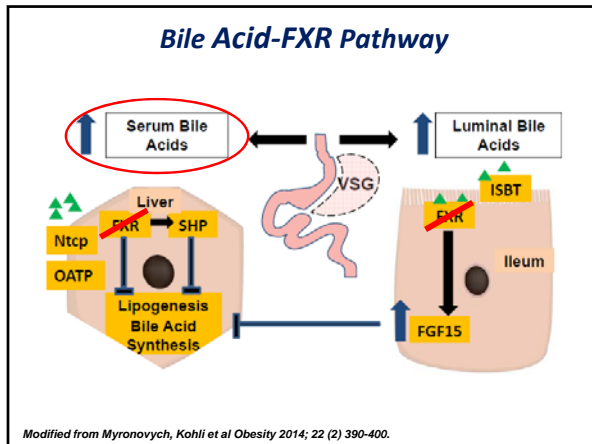
After VSG TUDCA is higher again!

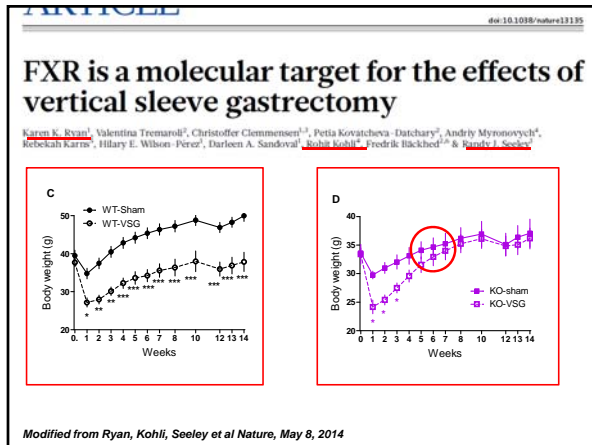


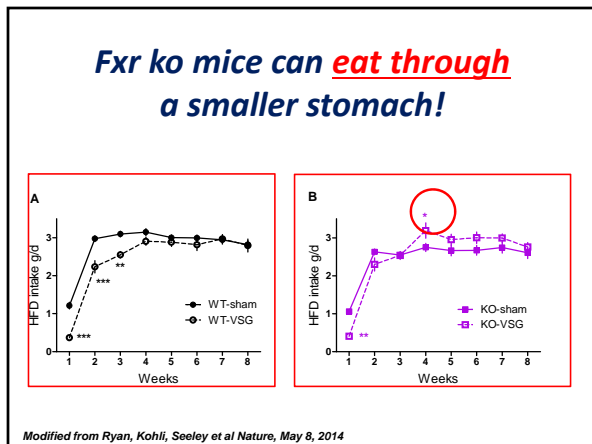
Myronovych, Kohli et al Obesity 2014; 22 (2) 390-400.

So why not just give TUDCA or GUDCA?

Bile Acid Diarrhea!

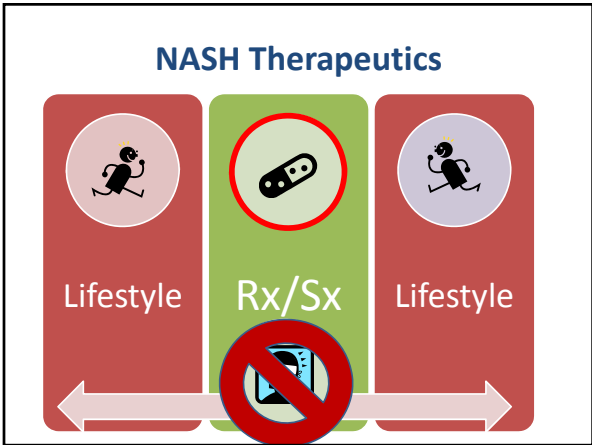






So is that it?

*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

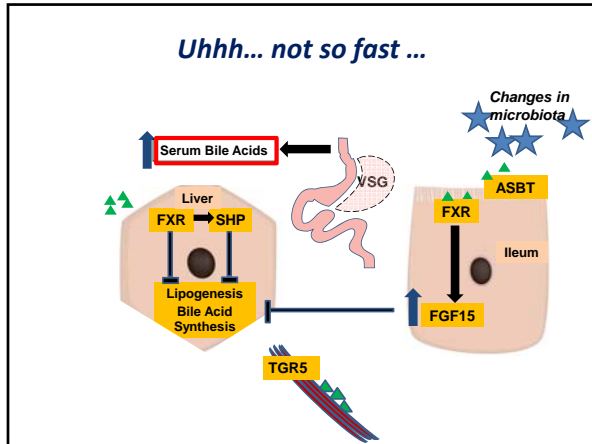
Prof Brent A Neuschwander-Tetri, MDCR^{1,2,3}, Rohit Loomba, MD, Prof Anus J Sanyal, MD, Prof Joel F Lavine, MD, Mark I Van Natta, MHS, Manal F Abdelmalek, MD, Prof Naga Chalasani, MD, Srinivasan Dasarthy, MD, Prof Anna Mae Diehl, MD, Bilal Hameed, MD, Prof Kris V Kowdley, MD, Prof Arthur McCullough, MD, Prof Norah Terrault, MD, Prof Jeanne M Clark, MD, Prof James Tenaclia, PhD, Prof Elizabeth M Brunt, MD, David E Kleiner, MD, Edward Doo, MD, for the NASH Clinical Research Network⁴

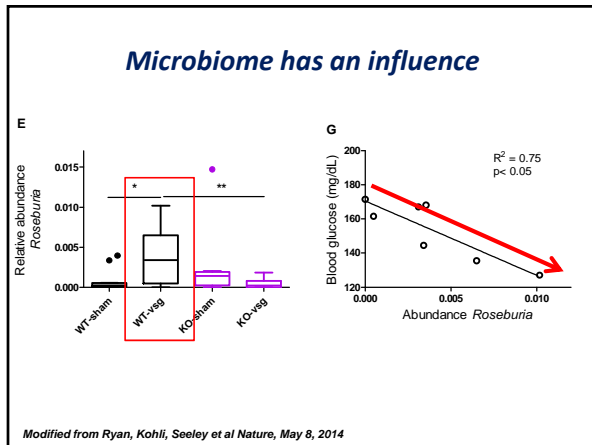
www.thelancet.com Vol 385 March 14, 2015

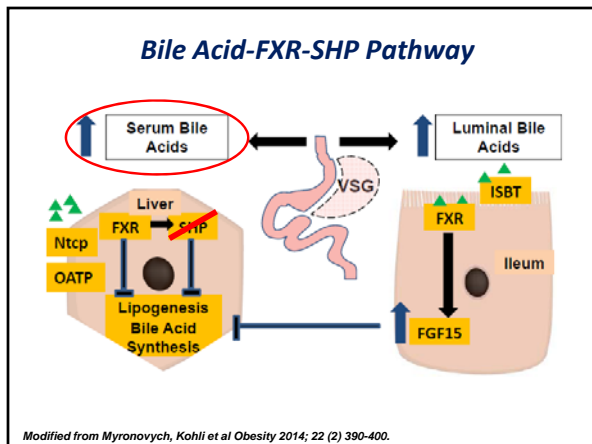
Obeticholic acid (OCA)
improved the histological features of NASH in adults

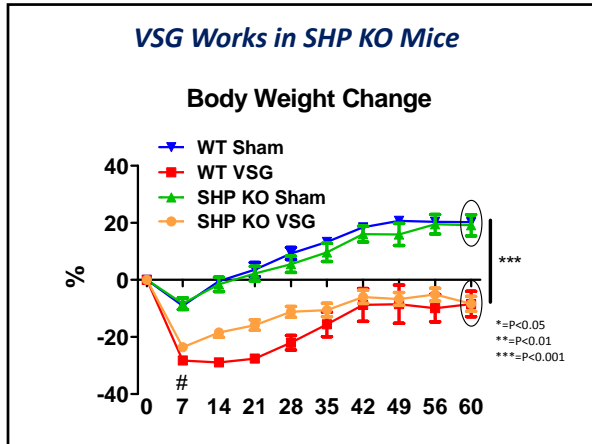
but

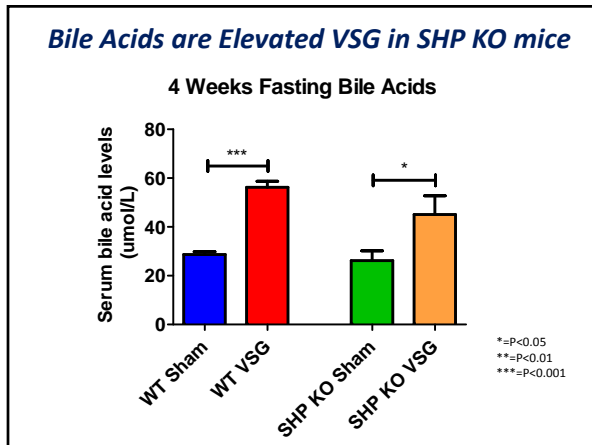
Decreased HDL
Increased LDL
NO Pediatric Data on OCA in NASH

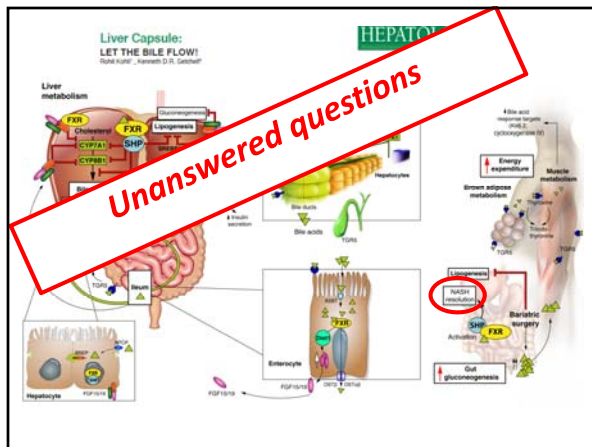














NIDDK- K08, R01
Ethicon Endo-Surgery
NASPGHAN Takeda
Prof. Kiewer, UTSW
Prof. Li Wang, Utah

