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NASH in IBD: A Grown Problem
An Additional Phenotype

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Disclosures

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Disclosures

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Author: Springer Publishing, Clinical Area – Liver disease
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Speaker Bureau: Mallinckrodt, Clinical Area – Hepatorenal Syndrome
Disclosure

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NASH in IBD: A Growing Problem
An Additional Phenotype

Cross Talk!
Objectives

1. Name the “Link” between NAFLD/NASH and IBD
2. Recognize the Roles of Secondary Bile Acid
3. Describe Unique Characteristic of the IBD - NAFLD/NASH Patient
4. Discuss Possible Predictors of NAFLD/ NASH in IBD Patients
NAFLD Prevalence

-30-45% US POPULATION
-70-90% OF OBESE & DIABETICS
>$3 Billion in Expenditures

Typical Risk Factors of NAFLD: METABOLIC SYNDROME

- Obesity
- Insulin Resistance
- Diabetes
- Dyslipidemia
- HTN
- Age
### Complex Pathogenesis

#### “MULTI-HIT” Phenomenon

| **Lipid Accumulation** | - Poor Diet & Inactivity  
- Increased De Novo Synthesis in Liver  
- DOWN reg B-Oxidation and UP Reg Insulin Resistance |
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<td><strong>Oxidative Stress and Hepatocyte Death</strong></td>
<td>- ER- Activates NF-KB Release and Remodeling</td>
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| **Cytokine Release** | - Kaupffer and Stellate Cells active IL-6, TNFa, IL-1B, TGF-B, along with TLR, NLR, JAK2, STAT3 signaling  
- Infiltration of MAC, DC, Tcells PMN & INSULIN RESISTANCE |
| **Organ X-talk** | - Adipose tissue is active, suppress B-oxidation and increase Insulin Resistance  
- Dysbiosis/ Translocation BA cant appropriately conjugate |

Complex Pathogenesis “MULTI-HIT” Phenomenon

**Lipid Accumulation**
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Prevalence of NAFLD by MS, Underweight and IBD

Metabolic Syndrome
- 19-34% by US
- 34-46% by BX

Underweight
- Underestimated
- Understudied
- Overlooked
- Prominent in Anorexia Nervous and AIDS population

IBD Patients
- 8-59%
  - 26-40% CD
  - 26-36% UC
- 6-10% Fibrosis
- 75% LEAN and UNDERWEIGHT

The Argument:

- Is the LEAN IBD Overlooked for NASH Evaluation?
- Why would this be?
- Should it become part of Health Maintenance in our GI assessment of IBD patient?

Who has IBD?
Who has NAFLD?
“Multi Hit” Pathogenesis of NAFLD

- Lipid Stores
- Cytokine Release
- Ox. Stress
- NAFLD
- Organ X-Talk
*Primary Bile Acids made in Liver

*Conjugate with Taurine and Glycine to Bile Salt drain trough CBD to Small intestine

*MICROBIOTA in Small intestine deconjugate to Secondary Bile Acids

Ileal Re-uptake

~5% Bile Acid loss in Stool

Creating Secondary Bile Acids

Liver

Cholesterol
  ↓
Hydroxycholesterol
  ↓

Primary bile acids
  (CA, CDCA, αMCA*, βMCA*)
  ↓

Hepatic conjugation
  (glycine, taurine)
  ↓

Bile salts
  (T(G)-CA, T(G)-CDCA, TαMCA*, TβMCA*)

  ↓

Deconjugation, enzymatic modifications (microbiota)

Secondary bile acids
  (CDCA, CA, DCA, LCA, UDCA, ωMCA*, HCA*, HDCA*, MDCA*)

Gut

Healthy Biome Promotes Deconjugation

- Bacteroides
- Bifidobacteria
- Proteobacteria
- Strepocaccacea
- Enterobacteriaceae
- Ruminococcacea

“Good Bacteria”

Organ Cross Talk

NAFLD
- BA limit TG synthesis
- Improve BG

IBD
- Limits Translocation
- Limits inappropriate Immune Response

HEALTHY BIOME
Cytokine Functions:
Secondary Bile Acid Functions – LIGANDS

Bile Acid Receptors are *Ligands for* **Hormones and Cytokines**

- **Farsenoid X**
  - Down regulates hepatic Lipid Production
  - Improves Insulin Signaling & B- Oxidation
  - Decrease expression of NF-KB, Inhibits TNF, IL1-B, II-6, MAC and DC signaling
  - Promotes Treg II-10

- **RORyx & GPBAR1**
  - Inhibits Transcription in TH17, TH1 pathway
  - Decrease IL-17A,II-23A, INF-y
  - Increase Treg
  - Inhibits NLR

Secondary BA Prevent NAFLD Progression

Secondary BA
Bind Receptor
Inhibit Inflammatory Cascade
Reduces Fatty Content & Modulates Insulin
Organ Cross Talk in the Pathogenesis of NAFLD

**Metabolic Syndrome**
- Dysbiosis
- **No Conjugation to Secondary Bile Acid**
- **No activation of Receptors**

**Crohns / Colitis**
- Ileal Surgical Resection or Inflammation
- Diminished BA Reuptake in Ileum & Liver
- Limited Receptor/Ligand Activation

**Organ X-talk is the Link!**
Typical Risk Factors of NAFLD
METABOLIC SYNDROME

Obesity
Insulin Resistance
HTN
Diabetes
Dyslipidemia
Age
Characteristic of IBD Patients With NAFLD

- Male Predominant
- CRP HIGH
- LFT/ PLATE WNL
- Younger < 45 yo
- Non-obese (BMI 22-26) =/-5kg

Proposed **Predictors** of NAFLD in IBD Patients

- Disease Activity
- Disease Duration
- Dysbiosis/Permeability
- Surgical Resection
- +/- Medications
- TPN

Milder IBD
1. < 1 Flare a year
2. Regardless of Metabolic Risk

Moderate IBD
1. > 1 Flare a year
2. Extensive geographic location
3. Severity
4. Surgical Intervention
5. Regardless of Metabolic Risk

S1, S2 Disease

S3 Disease

# Proposed Additional Mechanisms to Pathogenesis of IBD-NASH Phenotype

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<tr>
<th>Surgical Resection</th>
<th>Parenteral Nutrition</th>
<th>Medication</th>
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| **Interrupt Entero-Hepatic Circulation** | • Not Unique in IBD  
• Observed NAFLD by day 5 | • Corticosteroid  
– *Exacerbate* not cause |
| • 1*BA to 2* BA           |                                          | • MTX in RA *not IBD*             |
| – Deconjugation           |                                          | • Anti-TNF protects+/–            |
| • EFA & Carnitine Deficiency |                                      |                                   |

### IBD Medications

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<tr>
<th>Category</th>
<th>Medication</th>
<th>Effect</th>
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| **ANTI-TNF** | | • Shared Cytokine, Decreases proinflammatory signaling in the Stellate Cells and subsequent remodeling (NF-KB)  
• Indirectly Increases Insulin Signaling, result is improved Gluconeogenesis and B-oxidation |
| **IMM** | | • AZA may worsen  
• MTX 13.1mg/wk = in RA, NOT IBD |
| **Steroids** | | • Rodant Studies direct correlation, not Human  
• Exacerbate in Human |

Looking Ahead for the IBD Patient

EIM ?

Impact IBD TX?

?When Fibroscan

?MS NAFLD and TX
Summary

- NAFLD is not Limited to the Metabolic Syndrome Patient
- NAFLD has a Heterogenous Population and of Various Phenotypes
  - IBD = Non-obese < 45 yo, Male, LFT/PLATE wnl
- Early Screening is May Indicated In IBD
  - CD > UC

Will the Presences of NAFLD Change your Prescribing Practice in IBD?