METABOLIC SYNDROME AND HCV: FROM THEORY TO PRACTICE

HCV

Steatosis

Insulin resistance

Arun J Sanyal M.D.
Chairman, Div. of Gastroenterology, Hepatology and Nutrition
Virginia Commonwealth University
Richmond, VA

Conflicts: no financial relationships to declare for this presentation
Fatty Liver Disease in HCV

- Genotype 3
- In genotype 1
  - BMI
  - Diabetes
  - Insulin resistance
HCV virus and steatosis affect insulin resistance

Factors associated with IR:
- Age > 40
- Male gender
- genotype 1 and 4
- advanced fibrosis
- steatosis > 30%

Hepatitis C and the Metabolic Syndrome

- Insulin resistance and its consequences contribute to morbidity and mortality in patients with HCV.
- It is feasible to reduce the impact of insulin resistance and the metabolic syndrome on the burden of disease due to HCV.
How to diagnose steatosis vs steatohepatitis in a patient with HCV
## Effect of steatosis on HCV fibrosis: cross-sectional studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Effect of steatosis on fibrosis</th>
<th>Risk factors for fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adinolfi</td>
<td>↑</td>
<td>BMI, genotype 3</td>
</tr>
<tr>
<td>Hourigan</td>
<td>↑</td>
<td>BMI</td>
</tr>
<tr>
<td>Ruggiero</td>
<td>↑</td>
<td>BMI, genotype 3</td>
</tr>
<tr>
<td>Romero-Gomez</td>
<td>↑</td>
<td>Leptin, visceral obesity</td>
</tr>
<tr>
<td>Rubbia-Brandt</td>
<td>↑</td>
<td>Metavir activity</td>
</tr>
<tr>
<td>Ong</td>
<td>↑</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Sanyal</td>
<td>↑</td>
<td>Cytologic Ballooning</td>
</tr>
<tr>
<td>Patton</td>
<td>↑</td>
<td>BMI, HCV RNA</td>
</tr>
</tbody>
</table>
## Contribution of MetS and NAFLD to HCV-related burden of HCC

*Prevalence of HCC in HCV: 7.9/1000
Prevalence of HCC in NAFLD/NASH: 4.7/1000*

<table>
<thead>
<tr>
<th>Risk Factor (ICD-9-CM code)</th>
<th>HCC Patients (%)</th>
<th>Control (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV (070.41, 070.44, 070.51, 070.54, V02.62)</td>
<td>22</td>
<td>0.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>NAFLD/NASH (571.8, 571.9, 573.4, 573.8, 573.9)</td>
<td>54.6</td>
<td>2.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diabetes (250)</td>
<td>33.9</td>
<td>18.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Alcohol (571.0, 571.1, 571.2, 571.3)</td>
<td>11.6</td>
<td>0.2</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Sanyal et al, CMRO, 2010

Cirrhosis*: 69%
Diabetes: 32%
NASH: 68%

Cirrhosis*: 42%
Diabetes: 36%
HCV: 28%

HCV: 21%
NASH: 58%

*ICD-9-CM code 571.5 or 571.6
Insulin resistance and SVR

HCV genotype 1 subjects

Romero Gomez et al, Gastroenterology, 2005, 128:636-41

- HOMA > 2
- HOMA < 2

* P < 0.007
MicroRNAs and HCV

Steatosis

- / none

+ / none, weak

miR-122

Effect of interferon α and β

miR-1

miR-196

miR-296

miR-351

miR-448

HCV infection in cell culture (ref. 8)

HCV infection in human liver and in cell culture (ref. 9)

Pfeffer and Baumert, J Hepatology, 2008, 59:606-611
Impact of HCV on development of Type 2 Diabetes Mellitus

SVR decreases risk of type II diabetes mellitus

HCV: a risk factor for coronary artery disease

Butt et al, CID 2009:49 (15 July) • 225
Is HCV associated with dyslipidemia?

* p< 0.01
n= 89582 vs 82083

Butt et al, CID 2009:49 (15 July) • 225
Simple Lab tests are misleading for atherogenic risk in this population

N=50

Sd-LDL vs FLD activity (steatosis-ballooning-lob inflam) $r=0.53$, $p<0.0006$
HCV impairs survival

Survival Rate by HCV- vs. HCV+, unadjusted

N= 34480 in each group

Butt et al, HEPATOLOGY 2009;50:387-392
Hepatitis C and Metabolic Syndrome: Clinical implications

- Hepatitis C is associated with the metabolic syndrome

- Subjects with HCV have a higher risk of developing diabetes, chronic kidney disease, coronary artery disease

- In subjects with HCV, the presence of insulin resistance and MetS is associated with steatosis, increased progression to cirrhosis and HCC

- Insulin resistance confers resistance to PEG-IFN and ribavirin therapy
Insulin resistance: a vital physiologic phenomenon

Substrate

ADIPOCYTE

LIPID MOBILIZATION

LIPID STORAGE

Insulin-sensitizing cytokines (adiponectin)

Insulin-resistant cytokines (TNF-α)

β3-adrenergic neurons

Insulin catabolic hormones, cytokines
Pathogenesis of insulin resistance

Adipose tissue

Innate immune system activation:
Location
Diet
Gut flora
Leptin

Pro-inflammatory Cytokine profile

METABOLIC EFFECTS (insulin resistance)

Acute phase reaction

INFLAMMATION AND FIBROSIS
Pathophysiology of insulin resistance

Obesity, Genetics, Environment, Diet, Activity

(Insulin sensitivity vs resistance)

\[
\begin{align*}
& \uparrow \text{FFA} \\
\downarrow & \text{Met clearance} \\
& \uparrow \text{Glucose load} \\
& \downarrow \text{Hepatic glucose output} \\
& \downarrow \text{Hyperinsulinemia} \\
& \downarrow \text{Pancreatic exhaustion} \\
& \text{DIABETES MELLITUS}
\end{align*}
\]
Pathogenesis of NASH

- Insulin resistance
- FFA + insulin + cytokines
- Steatosis + metabolic dysregulation
  - ER stress
  - Oxidative stress
  - Inflammatory signaling
  - Mitochondrial injury
  - Apoptosis
  - Cell death
  - Stellate cell activation
  - Fibrosis

Multiple sources
Mechanisms of impaired insulin signaling in HCV

- Insulin
- Crk-Cbl
- GLUT translocation
- IRS
- PI3 kinase
- PKB
- SOCS
- TNF
- PTP-1B
- PTEN
- PP2a
- MAP kinase
- ras

Mechanisms of impaired insulin signaling in HCV
Hepatitis C and the Metabolic Syndrome

- Insulin resistance and its consequences contribute to morbidity and mortality in patients with HCV

- It is feasible to reduce the impact of insulin resistance and the metabolic syndrome on the burden of disease due to HCV
Hepatitis C and the Metabolic Syndrome: Implications for Management

• Assess presence of or risk of:
  – type 2 diabetes mellitus (www.diabetes.fi)
  – coronary artery disease

• Lifestyle intervention

• Drugs to prevent diabetes

• Drugs to prevent coronary artery disease

• Should insulin resistance be treated prior to anti-HCV treatment
Can diabetes be predicted by usual glycemic measures?

Biomarkers predictive of development of Type 2 diabetes

Performance of PreDx for prediction of Type 2 DM

Approaches to reduce risk of T2DM in subjects at risk

• Lifestyle changes:
  – 58% reduction with intense changes
  – 60% risk of new onset T2DM after intense intervention is stopped.

• Drugs:
  – Metformin
  – Glitazones
  – Acarbose

• Bariatric surgery (for BMI > 40 kg/m2)
Metformin: potential uses in HCV

Cufi et al, Cell Cycle 2010, 9:22, 4461-4468
Is metformin protective against HCC?

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Metformin (%)</th>
<th>Sufonylurea (%)</th>
<th>Insulin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>190</td>
<td>9.5</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>Controls</td>
<td>215</td>
<td>24</td>
<td>51</td>
<td>22</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>144</td>
<td>40</td>
<td>16</td>
<td>43</td>
</tr>
</tbody>
</table>

*Donadon et al, Liver Int. 2010 May;30(5):750-8.*
Approach to management of dyslipidemia

Estimate 10 yr risk of coronary heart disease
(lifestyle recommendations)

< 10%
LDL-c cutoff 190 mg/dl
Statins are first-line therapy
Statins are safe in patients with HCV
Statins may reduce inflammation and portal hypertension

10-20%
LDL-c cutoff 155 mg/dl

> 20%
LDL-c cutoff 115 mg/dl

ATP III recommendations for management of atherogenic dyslipidemia
Is Aspirin beneficial for prevention of cardiovascular events in diabetics

<table>
<thead>
<tr>
<th></th>
<th>Aspirin No of events</th>
<th>Control or placebo No of events</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ppp²²</td>
<td>3/246</td>
<td>8/251</td>
<td>0.38 (0.10 to 1.43)</td>
</tr>
<tr>
<td>ETDRS²¹</td>
<td>89/1031</td>
<td>128/1065</td>
<td>0.74 (0.59 to 0.94)</td>
</tr>
<tr>
<td>PHS¹⁷</td>
<td>11/275</td>
<td>26/258</td>
<td>0.40 (0.20 to 0.79)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>103/1552</td>
<td>162/1574</td>
<td>0.57 (0.34 to 0.94)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHS⁸</td>
<td>36/514</td>
<td>24/513</td>
<td>1.48 (0.88 to 2.49)</td>
</tr>
<tr>
<td>ppp²²</td>
<td>2/273</td>
<td>2/261</td>
<td>0.96 (0.14 to 6.74)</td>
</tr>
<tr>
<td>ETDRS²¹</td>
<td>81/825</td>
<td>100/790</td>
<td>0.91 (0.70 to 1.18)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>119/1612</td>
<td>126/1564</td>
<td>1.08 (0.71 to 1.65)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Aspirin No of events</th>
<th>Control or placebo No of events</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ppp²²</td>
<td>6/246</td>
<td>2/251</td>
<td>2.04 (0.38 to 11.04)</td>
</tr>
<tr>
<td>ETDRS²¹</td>
<td>45/1031</td>
<td>42/1065</td>
<td>1.07 (0.71 to 1.61)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>49/1277</td>
<td>44/1316</td>
<td>1.11 (0.75 to 1.64)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHS⁸</td>
<td>15/514</td>
<td>31/513</td>
<td>0.46 (0.25 to 0.85)</td>
</tr>
<tr>
<td>ppp²²</td>
<td>5/273</td>
<td>8/261</td>
<td>0.60 (0.20 to 1.80)</td>
</tr>
<tr>
<td>ETDRS²¹</td>
<td>38/825</td>
<td>30/790</td>
<td>1.31 (0.83 to 2.08)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>58/1612</td>
<td>69/1564</td>
<td>0.75 (0.37 to 1.53)</td>
</tr>
</tbody>
</table>

*DeBerardis et al, BMJ, BMJ 2009; 339:b4531*
Pioglitazone + PEG-IFN + Ribavirin for HCV

• N = 5
• All nonresponders
• Treated with pioglitazone (30 mg/day) + standard PEG/Riba
• None of the subjects responded although insulin sensitivity improved.

J Hep 2009
Future Directions

- Long-term studies to reduce the burden of non-hepatic complications related to MetS in subjects with HCV.
- Validation of the value of personalized approaches to reduce the risk of diabetes, CAD, HCC in subjects with HCV.
- Define the role of insulin resistance in treatment resistance to triple therapy.
- Define the role of modulating MetS to further boost the response to PEG-IFN and ribavirin.