Managing Hepatitis C and Diabetes: The Impact of a Cure

Disclosure Declaration

I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
Objectives
Pharmacists and Technicians

1. Identify risk factors for hepatitis C virus (HCV) exposure and the two-way association
2. Summarize the evidence and recommendations surrounding the co-management of HCV and diabetes
3. Recognize and be aware of potential drug interactions and contraindications for patients with HCV and diabetes

Outline

Pathophysiology and complications of HCV and diabetes

Overlapping risk factors

Current literature and research
   ◦ Effects of HCV on diabetes
   ◦ Impact of the cure

Recommendations and management
   ◦ Scenarios that could affect treatment

Pharmacotherapy and risk factors for drug-drug interactions
Question 1

_____ have increased risk of hepatocellular carcinoma.

A. GLP1s  
B. Sulfonylureas  
C. DPP4s  
D. DAAs

Question 2

The hepatitis C virus has been shown to infect the _____

A. Kidney  
B. Gallbladder  
C. Pancreas  
D. Brain
Question 3

Insulin resistance in hepatitis C only affects patients with diabetes

A. True
B. False

Viral Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of transmission</td>
<td>Fecal-oral</td>
<td>Bodily fluids</td>
<td>Bodily fluids</td>
</tr>
<tr>
<td>Acute/Chronic</td>
<td>Acute</td>
<td>Chronic</td>
<td>Chronic</td>
</tr>
<tr>
<td>Re-infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaccine?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>New cases in 2014</td>
<td>2,500</td>
<td>19,200</td>
<td>30,500</td>
</tr>
<tr>
<td>Total infections</td>
<td>-</td>
<td>850,000 – 2 million</td>
<td>2.7 – 4 million</td>
</tr>
<tr>
<td>Potential for Chronic Infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

"The ABCs of Hepatitis" CDC, 2016
Hepatitis C

- Most common infectious disease in the world
- Leading cause of hepatocellular carcinoma and liver transplantation
- Largely undiagnosed due to lack of symptoms
- 1945-1965 birth years
  - Make up 27% of US population but 75% of all HCV infections
- Changes in demographics


New Cases of Hepatitis C in Alaska

Alaska Reported  CDC Reported

Centers for Disease Control
Alaska Department of Health and Human Services
Behind the Data

HEPATITIS C AND OPIOID INJECTION ROSE DRAMATICALLY IN YOUNGER AMERICANS FROM 2004-2014

- Among people aged 18-29, HCV increased by 400% and admission for opioid injection by 622%
- Among people aged 30-39, HCV increased by 323% and admission for opioid injection by 83%

Source: Centers for Disease Control and Prevention and Substance Abuse and Mental Health Services Administration

Risk Factors for Hepatitis C

- IV drug misuse
- Born between 1945 – 1965
- Blood transfusions and hemodialysis
  - Before 1992
- Known exposures to HCV
  - Health care workers
- HIV infection
- Children born to HCV infected mothers
- Incarceration
- Intranasal drug misuse
- Body piercing or tattoos done with non-sterile instruments/ink

Diabetes

"I often say managing type 1 diabetes is like flying a plane. A plane is off-course most of the time and the pilot checks his instruments to bring it back on course. That’s type 1 diabetes."

Diabetes develops when glucose can’t enter the body’s cells to be used as fuel. This happens because either:

**In the case of Type 1 diabetes,** there is no key (insulin) to unlock the door to the cells.

**Or, in the case of Type 2 diabetes,** the key (insulin) is unable to unlock the door properly and/or the key (insulin) is there but the lock doesn’t work properly.
# Diabetes Data

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Alaska</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>7.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Incidence</td>
<td>6.0</td>
<td>7.9</td>
</tr>
<tr>
<td>High Blood Pressure</td>
<td>75.9</td>
<td>62.4</td>
</tr>
<tr>
<td>High Cholesterol</td>
<td>68.0</td>
<td>60.8</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>13.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>10.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Hospitalization*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>6.4</td>
<td>9.5</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Heart Attack</td>
<td>5.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Amputations</td>
<td>3.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Total Cost</td>
<td>865.5 million</td>
<td>42.2 billion</td>
</tr>
<tr>
<td>Years of Life Lost</td>
<td>4.7 years</td>
<td>4.4</td>
</tr>
</tbody>
</table>

*Centers for Disease Control Diabetes State Burden Toolkit*

# Risk Factors for Diabetes

- Age
- Sex
- Gestational diabetes
- Family history
- Hypertension
- Sedentary lifestyle
- Obesity
Risk Factors for Diabetes

- Age
- Sex
- Gestational diabetes
- Family history
- Hypertension
- Sedentary lifestyle
- Obesity

Risk Factors for Hepatitis C

- IV drug abuse
- Born between 1945 – 1965
- Blood transfusions and hemodialysis
- Health care workers
- HIV infection
- Children born to HCV infected mothers
- Incarceration
- Intranasal drug abuse
- Tattoos and piercings with unsterile tools

How Diabetes and Hepatitis C are Related

HCV positive patients are 2-3 times as likely to have diabetes
- Risk increases with length of infection and cirrhosis
- Regardless of other factors
  - BMI
  - Age
  - HBV
  - Liver diseases

The reverse is also true
- Increased prevalence of HCV in patients with diabetes compared to rest of population
- Patients with diabetes had poorer HCV outcomes

White et. al. Journal of Hepatology 2009
Hammerstad et. al. Frontiers of Endocrinology 2015
How Diabetes and Hepatitis C are Related

A Southeast Asian Study
- Differences between diabetic and non-diabetic patients with HCV
  - BMI was not statistically different between the two
  - Patients with diabetes were twice as likely to be cirrhotic (OR: 2.05, CI: 1.15-3.43)
  - Age, fasting blood sugar, cholesterol and renal function were different
- Limitations:
  - Size (361 patients), single center, external validity


How Diabetes and Hepatitis C are Related

Large 2018 meta analysis
- 31 studies
  - Diabetes was increased in patients with chronic hepatitis C and cirrhotic hepatitis C
  - Risk was also increased in cirrhotic patients
  - “On the whole the results show an unequivocal association of HCV chronic infection and T2DM.”

Fabiani et. al. Reviews in Endocrine and Metabolic Disorders, 2018
The Two Way Association

Same meta analysis
- The prevalence of HCV infection in diabetic patients is higher than in non-diabetic
- Diabetes seems to have an impact on hepatocellular carcinoma (HCC) development

The prevalence of T2D was shown to increase with every rise in the fibrosis score of HCV patients with an OR of 3.83
Hepatitis C Virus

RNA virus
- 10 proteins

6 genotypes multiple subtypes

Genotype matters
- Prevalence
- Outcomes
- Treatment
- Mixed infections

Acute Infection vs Chronic Infection

Acute infection – mostly asymptomatic
- Unlikely to lead to diagnosis
- 15-25% of patients can clear the disease and have undetectable virus
  - Depends on age, sex, genetic polymorphisms, and liver enzymes

Chronic infection
- Presence of HCV after 6 months
- Left untreated leads to long term liver cirrhosis and death
  - After 20 years of infection, 20% of patients will die from HCC
- Rate of progression to cirrhosis varies
  - Males, age over 50, alcohol use, coinfection and immunosuppression

Centers for Disease Control, 2018
Liver Fibrosis and Cirrhosis

As virus infects and spreads in the liver, hepatic stellate cells (HSC) are activated
◦ Leads to proliferation of myofibroblasts

Fibrosis
◦ Reversible wound healing
◦ Due to cell regeneration the deposition of extracellular matrix (ECM) is reduced

Progression of fibrosis to cirrhosis
◦ Increasing damage leads to disruption in the equilibrium between deposition and dissolution of ECM proteins

Insulin Resistance in Hepatitis C

Insulin resistance is significantly increased in patients with HCV
Prospective case–control study of 133 patients with advanced liver fibrosis (F3–F4) without type 2 diabetes
At baseline patients had similar liver fibrosis levels
Homeostatic model assessment for insulin resistance
Pretreatment HOMA-IR was $4.90 \pm 4.62$
Post-treatment HOMA-IR was $2.38 \pm 1.642$
◦ $p<0.0001$

Adinolfi et. al. Journal of Gastroenterology and Hepatology, 2017
However, the Exact Mechanism is Unknown

Increase in reactive oxygen species
- NS3 and NS5, in particular, were shown to trigger oxidative stress responses.
- leads to the release of an array of cytokines, including TNFα, TGFβ, IL-6, and IL-8.

TNF-α and other inflammatory cytokines
- Higher serum TNFα in diabetic HCV patients than in non-diabetic HCV patients (74 vs 64%; p-value <0.0001)

Beta cell dysfunction
- Pancreatic β-cells are infected with HCV and have morphological and functional defects, including a blunted insulin response to glucose

Hammerstad et al. Frontiers of Endocrinology 2015
Hepatitis C Treatment

Direct Acting Antivirals (DAA)
- Highly effective
- Treatment and duration is dependent on:
  - Genotype and subtype
  - Presence of cirrhosis
  - Treatment naïve or treatment experienced
  - Race
  - Recommended drug
  - Other disease states
  - Viral load

### Table

<table>
<thead>
<tr>
<th></th>
<th>Protease inhibitors</th>
<th>Nucleos(t)ide polymerase inhibitors</th>
<th>Non-nucleoside polymerase inhibitors</th>
<th>NSSA inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potency</strong></td>
<td>High (varies by HCV genotype)</td>
<td>Moderate-to-high (consistent across HCV genotypes and subtypes)</td>
<td>Varies by HCV genotype</td>
<td>High (against multiple HCV genotypes)</td>
</tr>
<tr>
<td><strong>Barrier to resistance</strong></td>
<td>Low (1a &lt; 1b)</td>
<td>High (1a = 1b)</td>
<td>Very low (1a &lt; 1b)</td>
<td>Low (1a &lt; 1b)</td>
</tr>
<tr>
<td><strong>Potential for drug interactions</strong></td>
<td>High</td>
<td>Low</td>
<td>Variable</td>
<td>Low-to-moderate</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Rash, anemia, ↑ bilirubin</td>
<td>Mitochondrial toxicity, interactions with HIV antiretrovirals (nucleoside reverse transcriptase inhibitors) and ribavirin*</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Daily to three times daily</td>
<td>Daily to twice daily</td>
<td>Daily to three times daily</td>
<td>Daily</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>Later generation protease inhibitors are expected to have higher barriers to resistance and be pan-genotype</td>
<td>Single target for binding at the active site</td>
<td>Many targets for binding at allosteric sites</td>
<td>Multiple antiviral mechanisms of action</td>
</tr>
</tbody>
</table>

### Outcomes in Patients with HCV and Diabetes

Overall, most studies support the notion that insulin resistance (IR) and diabetes predispose to liver fibrosis and cirrhosis.

HCV patients with diabetes had a hazard ratio of 1.73 for HCC compared to non-diabetic HCV patients.

A recent meta-analysis of 14 studies showed that patients with IR treated with peg IFN–RBV had a 20% lower rate of SVR compared to patients without IR (95% CI: –29.9 to –9.4%, p < 0.001).

- In addition, responders had a lower HOMA-IR compared to non-responders (mean difference: –0.92, 95% CI: –1.53 to –0.32, p < 0.001)

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Deltenre et al. Journal of Hepatology, 2011
Guideline Recommendations

American Association for the Study of Liver Diseases (AASLD)
- The relationship between chronic hepatitis C and diabetes (most notably type 2 diabetes and insulin resistance) is complex and incompletely understood.
- Treatment should be initiated as early as possible to reduce insulin resistance, liver fibrosis and hepatocellular carcinoma.

American Gastroenterological Association
- Until more data become available to provide evidence-based recommendations for addressing diabetes and fatty liver in patients post-SVR, patients at risk or with a known diagnosis should be advised of the risk of liver-related complications, and continue disease-specific management to optimize weight loss and glycemic control.

Screening and Therapeutic Considerations

Literature commonly recommends screening for diabetes in all HCV patients

Screening diabetic patients at risk is also reasonable
- Persistently elevated ALT
- Or in cases that do not have evidence of non alcoholic fatty liver disease
Treatment Considerations

Not much room for change in HCV treatment

What about diabetes treatment?

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Therapy Considerations

Metformin is still the drug of choice
- increasing evidence that metformin is independently associated with reduced risk for HCC and liver-related death/transplantation
- not recommended in advanced hepatic disease because of increased risk for lactic acidosis

Interestingly, GLP-1 levels were decreased and DPP-4 levels are significantly increased in HCV patients
- Does not affect

Small study in Japan found that insulin and second-generation SU were independent variables associated with incidence of HCC
Impact of Curing Hepatitis C

Treating HCV and achieving SVR impacts insulin resistance and glycemic control

But...

SVR may decrease medication needs in patients cleared of HCV

Post SVR hepatocellular carcinoma is still increased in patients with diabetes

Patients without diabetes have a 70% decrease in HCC risk

Positive Glycemic Results from Treatment

Improvement in Glycemic Control of Type 2 Diabetes After Successful Treatment of Hepatitis C Virus

Large Veteran’s Affair’s study showed improvement in HgbA1c

- 2,435 patients with diabetes who underwent interferon-free and ribavirin-free DAA-based antiviral treatment for HCV
- Average A1c of 7.2%
- The mean of the HbA1c measurements of patients was calculated for the 12-month period prior to treatment (“pretreatment”) and the 12-month period from 3 to 15 months after treatment (“post-treatment”).

Results showed patients had a decrease in A1c, insulin use and metformin use

- Were less likely to receive antidiabetic medication (74.8% vs 78.0%) or insulin (41.3% vs 49.8%) – not significant
- The number of patients receiving treatment with insulin decreased more significantly in patients who achieved SVR (from 41.3% to 38%) than in patients who did not (who actually had a slight increase in the proportion of patients receiving treatment with insulin)
- Amount not reported

Hum et al. Diabetes Care, 2017
Positive Glycemic Results from Treatment

There was a significant drop in fasting glucose in the group of patients who received treatment compared to the group that received placebo.

In overall, notable drop in fasting glucose was observed (~8.87 mg/dL by week 12; p < 0.0001).

The most significant drop in fasting glucose was recorded in the group of patients with type II diabetes (~22.1 mg/dL by week 12; p < 0.0001).

Followed by still significant drop of fasting glucose in the group of patients with pre-diabetes (~5.78 mg/dL by week 12; p < 0.0001).

On the contrary, there was slight, not significant increase of fasting glucose in the group of patients with normal baseline fasting glucose levels (1.34 mg/dL by week 12; p = 0.057)
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Ethnicity</th>
<th>HCV Genotype</th>
<th>DAA Treatment</th>
<th>Virologic Response</th>
<th>Metabolic Response</th>
<th>SVR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales, 2016</td>
<td>USA</td>
<td>T2DM</td>
<td>Mostly genotype 1</td>
<td>Only sofosbuvir based</td>
<td>NA</td>
<td>Yes</td>
<td>25%</td>
</tr>
<tr>
<td>Ciancio, 2018</td>
<td>Italy</td>
<td>T2DM</td>
<td>Mostly genotype 1</td>
<td>Mostly sofosbuvir based</td>
<td>Yes</td>
<td>Yes</td>
<td>21%</td>
</tr>
<tr>
<td>Fabrizio, 2017</td>
<td>Italy</td>
<td>T2DM</td>
<td>Mostly genotype 1</td>
<td>Mostly sofosbuvir based</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pavone, 2016</td>
<td>Italy</td>
<td>T2DM</td>
<td>Mostly genotype 1</td>
<td>Mostly sofosbuvir based</td>
<td>Yes</td>
<td>Yes</td>
<td>23%</td>
</tr>
<tr>
<td>Abdel Alem, 2017</td>
<td>Egypt</td>
<td>T2DM</td>
<td>Mostly genotype 4</td>
<td>Only sofosbuvir based</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
</tr>
<tr>
<td>Dawood, 2017</td>
<td>Egypt</td>
<td>T2DM</td>
<td>Genotype 4</td>
<td>Sofosbuvir + daclatasvir</td>
<td>Yes</td>
<td>Yes</td>
<td>27%</td>
</tr>
<tr>
<td>El Saghier, 2018</td>
<td>Egypt</td>
<td>T2DM</td>
<td>Genotype 4</td>
<td>Sofosbuvir + simeprevir</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Beig, 2018</td>
<td>New Zealand</td>
<td>LTx patients, only patients without antidiabetic treatment</td>
<td>Mostly genotype 1</td>
<td>Mostly sofosbuvir based</td>
<td>yes</td>
<td>Yes</td>
<td>40%</td>
</tr>
<tr>
<td>Chaudhury, 2017</td>
<td>USA</td>
<td>General population, 3% HIV positive, 17% T2DM</td>
<td>Genotype 1</td>
<td>Multiple DAA</td>
<td>NA</td>
<td>No</td>
<td>3%</td>
</tr>
</tbody>
</table>

NA: not available; T2DM: type 2 diabetes mellitus.

**HCV**

- Direct interference with insulin signaling
- Secretion of soluble mediators
- Systemic chronic inflammation
- Chronic endothelial damage
- Direct infection of arterial wall (?)
- Virus induced hypolipidemia (?)

**Hepatic IR**

- Type 2 diabetes
- Liver fibrosis
- HCC
- Poor response to IFN alpha

**Peripheral IR**

- Atherosclerosis

**Cardio- & cerebrovascular vascular disease**

**Protective (?)**
Some Interesting Studies

Meta-analysis of 34 studies, all of which followed patients with coronary artery disease, unstable angina pectoris, myocardial infarction, and stroke, patients with chronic HCV infection were at significantly higher risk for cardio-cerebrovascular disease than noninfected patients (OR: 1.43; 95%CI: 1.21 - 1.68).

Petta et al. Journal of Hepatology, 2018

Direct Acting Antivirals and Interactions

DAAs have many interactions with medications that are common used for diabetes
- Statins
- Antiplatelet therapy

Other common medications
- Acid lowering agents
- Analgesics
- Macrolides

Less common medications
- Antiarrhythmic
- Anticoagulants
- Anticonvulsants
Role of the Pharmacy

Depending on practice site
- Transitions of care
- Continuous follow up and education
  - Adherence
  - Administration
  - Adverse reactions
- Monitoring interactions
  - Drugs
  - Herbal products

Behind the scenes factors
- Prior authorization
- Billing and reimbursement

Resources

Interaction checkers
- Hep Drug Interactions
  - Comprehensive check for large number of drugs
  - Provides potential actions to take
  - Individualized patient reports
  - https://www.hep-druginteractions.org/
- Hepatitis C Online
  - Funded by CDC and ran by universities
  - Large collection of drug guides
  - Free modules and CE in HCV topics
  - Clinical tools and calculators
  - https://www.hepatitisc.uw.edu/
Elbasvir-Grazoprevir [Zepatier]
One Nambi EBB-GEZ

Self-Study Modules and Sections

1. Screening and Diagnosis of Hepatitis C Infection
2. Evaluation, Staging, and Monitoring of Chronic Hepatitis C Infection
3. Management of Cirrhosis-Related Complications
4. Evaluation and Preparation for Hepatitis C Treatment
5. Treatment of Chronic Hepatitis C Infection
6. Treatment of Key Populations and Unique Situations

Elbasvir-Grazoprevir is approved for the treatment of chronic hepatitis C infection in adults 18 years of age or older with genotype 1 infection, including patients with prior null response or relapse following prior treatment with a NS5A inhibitor. It is also approved for the treatment of genotype 1 infection in patients who have previously been treated with a regimen containing a protease inhibitor due to RBV intolerance or suboptimal response.

For patients with cirrhosis or with BMI >35, a lower weight-based dose of elbasvir and grazoprevir should be considered. In addition, patients with decompensated cirrhosis should be monitored closely and have close follow-up with their healthcare provider.

About This Topic

Learning Objectives

1. Describe the diagnostic and treatment options for chronic hepatitis C infection.
2. Discuss the potential benefits and risks of elbasvir and grazoprevir, including its efficacy, safety, and tolerability.
3. Understand the importance of monitoring and managing potential side effects during treatment.

Activities in This Topic

1. Practice Management of Hepatitis C Infection
2. Improve Treatment of Hepatitis C Infection
3. Evaluate and Prepare for Hepatitis C Treatment
4. Treat Hepatitis C With Antivirals

CAGE Questionnaire

AUDIT-C Questionnaire

Currents

Audit

1. Hematopoietic stem cell transplantation for patients with chronic hepatitis C infection
2. Use of IFN-free regimens in patients with compensated cirrhosis
3. Use of direct-acting antivirals in patients with decompensated cirrhosis

Data on file.
Question 1

_____ have increased risk of hepatocellular carcinoma.

A. GLP1s
B. Sulfonylureas
C. DPP4s
D. DAAs
Question 2

The hepatitis C virus has been shown to infect the _____

A. Kidney
B. Gallbladder
C. Pancreas
D. Brain
Question 3

Insulin resistance in hepatitis C only affects patients with diabetes

A. True
B. False
Summary

There is a two way association between hepatitis C and diabetes
- There is a higher prevalence of diabetes in patients with HCV
- Diabetes increases the risk of poor outcomes from HCV

HCV is associated with insulin resistance
- Including non-diabetic patients

Treating HCV provides some benefit to glycemic control

More data is needed for formal guideline recommendations

References


References


Questions?