Diabetes & Hepatitis C Virus Infection

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Outcomes of hepatitis C treatment on type 2 diabetes. How different is managing type 2 diabetes before and after hepatitis elimination?

Pre-test

Achieving sustained viral remission (SVR) with treatment of HCV

A. Often results in weight gain that can worsen diabetes control
B. Can worsen insulin resistance (IR) and hyperglycemia
C. Can reduce insulin resistance and hyperglycemia
D. Is most effective in those with more extensive hepatic fibrosis

Background: Hepatitis C Overview

- Hepatitis C is a liver infection caused by the hepatitis C virus (HCV).
- Hepatitis C is spread through contact with blood from an infected person
  - Most people become infected with the hepatitis C virus by sharing needles or other equipment used to prepare and inject drugs*
- For more than half of people who become infected with the hepatitis C virus, it becomes a long-term, chronic infection.
  - Chronic hepatitis C can result in serious, even life-threatening health problems like cirrhosis and liver cancer
  - Chronic hepatitis C can be considered metabolic disorder with abnormal lipid and glucose metabolism (IR and DM are now considered *extrahepatic manifestations* of HCV)**
  - People with chronic hepatitis C often have no symptoms
- Getting tested for hepatitis C is important, because treatments can *cure* most people with hepatitis C in 8 to 12 weeks.

*Transmission of HCV

HCV is transmitted primarily through parenteral exposures to infectious blood or body fluids that contain blood.

- Possible exposures include
  - Injection-drug use (currently the most common mode of HCV transmission in the US)
  - Birth to an HCV-infected mother
- Although less frequent, HCV can also be spread through:
  - Sex with an HCV-infected person (an inefficient means of transmission, although HIV-infected men who have sex with men [MSM] have increased risk of sexual transmission)
  - Sharing personal items contaminated with infectious blood, such as razors or toothbrushes
  - Other health-care procedures that involve invasive procedures, such as injections (usually recognized in the context of outbreaks)
  - Unregulated tattooing
  - Receipt of donated blood, blood products, and organs (rare in the United States since blood screening became available in 1992)
  - Needlestick injuries in health-care settings

**Extrahepatic Manifestations of HCV Infection

- Cryoglobulinemic vasculitis
- Membranoproliferative glomerulonephritis
- Membranous nephropathy
- Monoclonal gammopathy
- Non-Hodgkin lymphoma
- Arthralgia/arthritis
- Raynaud phenomenon
- Fatigue
- Sicca syndrome
- Lichen planus
- Porphyria cutanea tarda
- **Diabetes mellitus/insulin resistance**
- Hypothyroidism/hyperthyroidism

What are the chances of someone with HCV infection developing cirrhosis or liver cancer?

- Of every 100 people infected with HCV, approximately 5–25 will develop cirrhosis within 10–20 years. Patients who develop cirrhosis have
  - a 1%–4% (~3%) annual risk of developing hepatocellular carcinoma (HCC)
  - a 3%–6% annual risk of hepatic decompensation
    - the risk of death in the following year is 15%–20%
- Rates of progression to cirrhosis are increased in the presence of a variety of factors, including
  - Being male
  - Being age >50 years
  - Consuming alcohol
  - Having nonalcoholic fatty liver disease, hepatitis B, or HIV coinfection
  - Receiving immunosuppressive therapy
  - Having **diabetes** (also increases risk of decompensated cirrhosis)

Diabetes *aggravates* liver disease…

- Inflammation and ***fibrosis*** (cirrhosis) are enhanced by diabetes
  - which may promote liver damage through various cytokines and proinflammatory factors
- Diabetes is an independent predictor of ***decompensation*** in liver disease *(decompensated cirrhosis)*
  - Diabetes is associated with ascites, hepatic encephalopathy, variceal hemorrhage, spontaneous bacterial peritonitis, renal dysfunction, and **hepatocellular cancer (HCC)**

type 2 DM is a risk factor for chronic liver disease

Liver disease can induce or aggravate diabetes…

- Diabetes can occur as a complication of cirrhosis, known as hepatogenous diabetes (HD) (Cirrhosis is diabetogenic) (see recording and/or slide deck of July 2020 ECHO didactic Diabetes & Cirrhosis https://www.indiancountryecho.org/resources/diabetes-and-cirrhosis/)
  - Most people with cirrhosis have impairment of glucose tolerance
    - Clinically overt diabetes is present in **30 %** of patients with liver cirrhosis
    - **80%** of patients with *normal fasting blood glucose* show impaired glucose tolerance or diabetes by means of an oral glucose tolerance test (OGTT)
  - The prevalence of **diabetes is significantly higher** among patients with **HCV cirrhosis** than in patients with cirrhosis due to other etiologies
    - Most studies have noted a 2- to 10-fold increase of T2D in chronic HCV infection compared to other liver diseases

Sort of a vicious circle –

Insulin resistance increases steatosis & fibrosis

and

Steatosis & fibrosis increase insulin resistance

People with HCV more likely to get Diabetes

- Age (>40)
- Longer duration of chronic HCV
- Male (males also increased fibrosis/cirrhosis)
- Family history of T2D
- HCV Genotype (2>1>3)
- Cirrhosis/high fibrosis score
- Lack of response to HCV treatment (lack of SVR)
  - diabetes increased risk of treatment failure to older Rx options (interferon)

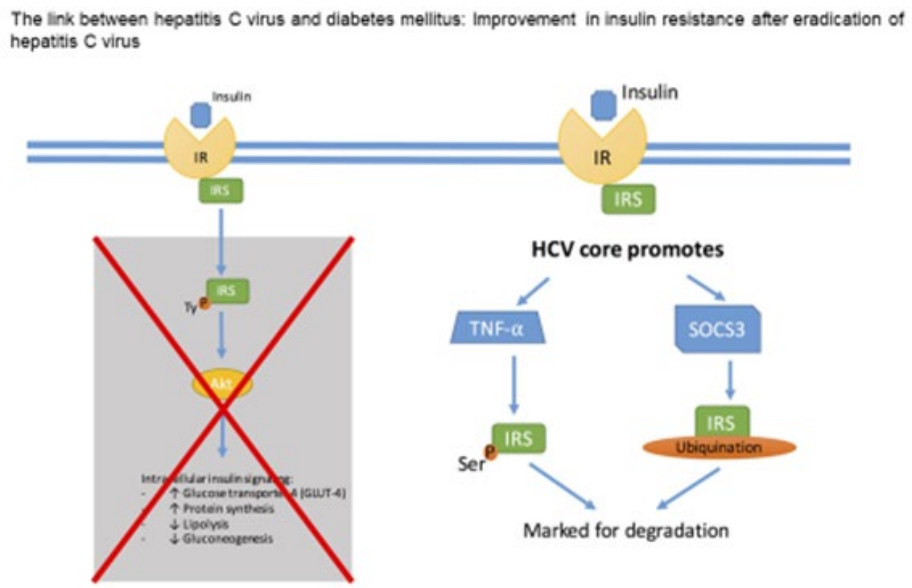
Chronic HCV can induce or aggravate diabetes…

- Prospective studies have described the association between diabetes and chronic infection of the liver by HCV
  - It is estimated that up to 33% of chronic hepatitis C patients have T2D
    - HCV infection *precedes* the diagnosis of T2D in as many as 73% of cases
  - Individuals with ***chronic HCV infection*** had a **threefold risk** of developing **diabetes** compared to those *without hepatitis*
    - This association has been described in **both cirrhotic and in non-cirrhotic** patients with HCV infection
    - The reported prevalence of diabetes in ***noncirrhotic*** HCV patients was 12.6–17 % - indicating it is not just due to the diabetogenic effect of cirrhosis

Evidences indicates that **HCV may *directly* induce metabolic disturbances** leading to impaired glucose tolerance and steatosis

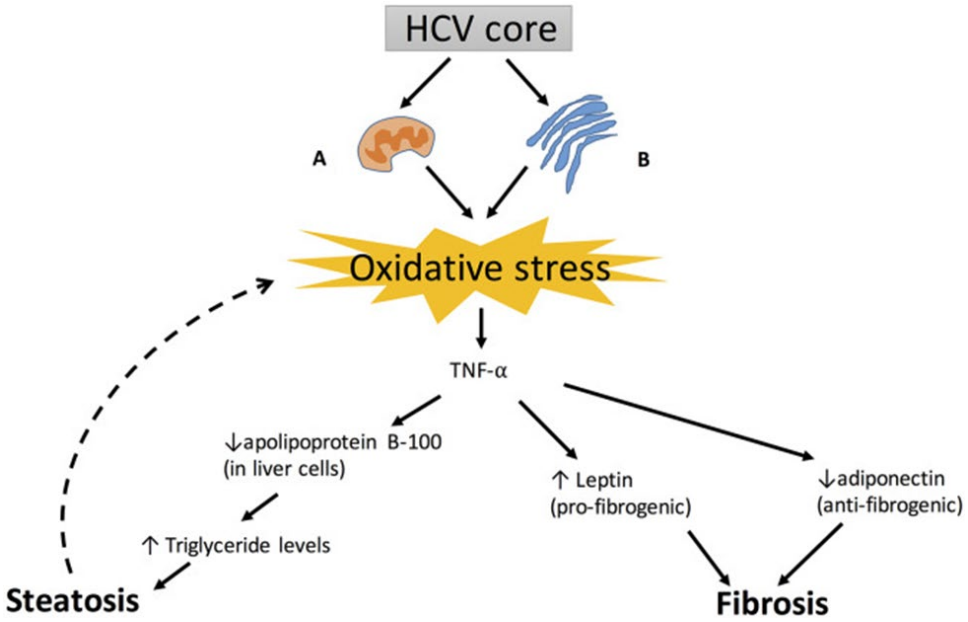
Molecular Mechanisms by which HCV infection might increase the risk for development of T2DM or worsen glycemic control in patients with established T2DM.

- HCV core protein in the hepatocyte
  - upregulates tumor necrosis factor α (TNF-α), which causes the phosphorylation of the IRS-1/IRS-2 at a serine amino acid and marks the IRS-1/IRS-2 for **degradation** &
  - upregulates suppressor of cytokine signaling 3 (SOCS3). SOCS3 leads to the ubiquitination of IRS1/IRS-2, which marks the substrate for **degradation** *preventing interaction with the insulin receptor*, resulting in a *blockage of glucose uptake at the cellular level* **(Insulin Resistance)**



Molecular Mechanisms by which HCV infection might increase the risk for development of T2DM or worsen glycemic control in patients with established T2DM.

- HCV core protein leads to oxidative stress by causing dysfunction at the *mitochondria* and endoplasmic reticulum (ER) of hepatocytes - oxidative stress increases ***inflammatory cytokines*** such as **TNF-α**, which
  - promotes a state of **hyperinsulinemia**, decreases apolipoprotein B-100, enhances triglyceride accumulation in the liver, and leads to **steatosis**, which in turn creates more oxidative stress.
  - increases leptin, a profibrogenic hormone, and decreases adiponectin, an antifibrogenic hormone, eventually contributing to **fibrosis** of the liver



Beta Cell Dysfunction & Impaired Insulin Release

- HCV can have a *direct cytotoxic effect* of HCV on pancreatic islet cells
  - HCV-infected beta cells have been noted to have both morphological and functional defects, including a ***blunted insulin response to glucose***
- *Proinflammatory cytokines* secreted in chronically infected HCV patients, such as TNFα, may also affect beta cell function by disrupting insulin signaling/secretion and by sensitizing the beta cell to the toxic effects of free radicals
- Altered incretin expression of Incretins with HCV infection.
  - Decreased level of glucagon-like peptide (GLP)-1 (which promote insulin biosynthesis, insulin secretion, and ß-cell survival)
  - Upregulation of liver and ileum dipeptidyl peptidase (DPP)-IV expression (which inactivate GLP-1)

These findings support the notion that HCV infection induces significant **beta cell dysfunction** either directly or through cytokine release or reduction in GLP-1

Attenuated Diabetic Phenotype with HCV

- Patients with HCV infection show an attenuated diabetic phenotype compared with that observed in patients without HCV infection –
  - phenotype intermediate between type 1 and type 2 DM
  - often leaner
  - can have significantly *lower* total and low-density lipoprotein (LDL) cholesterol levels
    - This is due to **HCV-induced hypobetalipoproteinemia** because of binding competition between HCV and the hepatic LDL receptor
    - This can also give rise to steatosis – chronic HCV patients have a 30–70 % prevalence of **hepatic steatosis**
- HCV infection can be associated with autoimmune phenomena, including type 1 diabetes (T1D) (much less common)

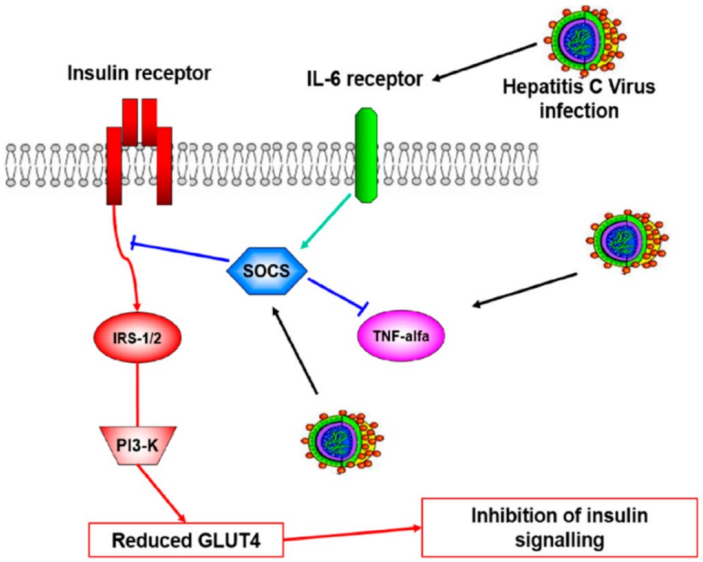
Autoimmune T1D associated with HCV

- HCV is also known to be associated with several autoimmune manifestations, including type 1 diabetes (T1D).
  - Massive stimulation of the immune system induced by viral infection may result in the **nonspecific activation** of potentially self-reactive lymphocytes that might develop autoimmunity, inducing an *immune cascade* that could culminate in islet cell dysfunction in susceptible individuals
- Therapy for chronic HCV infection with interferon alpha (IFNα), can also trigger autoimmune diabetes.
  - The immunomodulatory effect of IFNα can induce or exacerbate autoimmune diseases – most likely IFNα triggers or accelerates autoimmunity in *genetically susceptible* individuals
    - interferon-induced thyroiditis (IIT) is the most frequently reported autoimmune complication of IFNα therapy
    - other autoimmune conditions, such as **T1D**, systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia, optic neuritis, vitiligo, and autoimmune hemolytic anemia are also associated

Treatment of HCV & Potential Impact on Diabetes

- Therapies to *reduce HCV viral load*, inflammation, steatosis, and TNF-a activity can be *expected* to improve metabolic parameters and reduce DM risk in patients with chronic HCV.

- In 1990s to early 2000s, Interferon, combination interferon plus ribavirin (RBV) and pegylated interferon plus RBV increased ***sustained virologic response (SVR)*** rates from ~5% to ~40-80%
  - People with ***IR or diabetes had a worse virologic response*** to Interferon based HCV Rx, but if responded showed a reduced risk of diabetes or improved glycemia
- After 2000, the advent of **direct-acting antivirals (DAAs)** has brought about a renaissance in the treatment of chronic hepatitis C virus (HCV) infection
  - SVR rates now routinely >90%
  - Success of direct-acting, antiviral-based therapy for chronic hepatitis C is ***not affected by type 2 diabetes***



Outcomes of hepatitis C treatment on type 2 diabetes. How different is managing type 2 diabetes before and after hepatitis elimination?

- Lit search
  - Many case / cohort reports

Systematic Review:

The Effect of Viral Clearance Achieved by Direct-Acting Antiviral Agents on Hepatitis C Virus Positive Patients with Type 2 Diabetes Mellitus: A Word of Caution after the Initial Enthusiasm

J of Clin Med Feb 2020

- (1) Does SVR achieved by DAAs significantly *prevent the onset* of IR and DM?
- (2) Does HCV clearance with DAAs lead to significant improvement of glycol-metabolic control in patients with diabetes? If so, is this control maintained over the long term?
- (3) Does SVR-related glycol-metabolic improvement induce de-escalation/withdrawal of antidiabetic therapy?
- (4) Do DAA-induced glycemic changes determine a significant clinical impact on the outcome of diabetes and its complications?
- (5) What is the clinical impact of DAA-induced SVR on the incidence of HCC in diabetic patients?

1) Does SVR Achieved by DAAs Significantly *Prevent* the Onset of Insulin Resistance and DM?

- In the pre-DAA era, several reviews and meta-analyses showed that SVR reduced the incidence of IR and diabetes in cured patients.
- This observation was confirmed by most of the studies conducted on patients who were treated with DAAs indicating a ***beneficial effect of SVR in reducing the risk of onset of IR/DM***
  - However, appropriate follow-up is still lacking so that definite *conclusions cannot* be drawn on the *lasting efficacy* of antiviral therapy with DAAs regarding the incidence of glycometabolic abnormalities
  - Also, most studies had no data regarding possible *confounding factors* such as changes in lifestyle (diet, exercise, smoking status, weight changes)

2) Does HCV Clearance with DAAs Lead to Significant Improvement of Glycometabolic Control in Patients *with Diabetes*? If so, is This Control Maintained over the Long Term?

- In conclusion, most studies published so far show an **improvement of glycometabolic control** at the end of therapy or in the immediate post-therapy months in diabetic patients, or in some subgroups.
  - Whether this beneficial effect is maintained over the long term is still a matter of debate.
    - For this reason, large prospective cohort studies with appropriate analysis of possible *confounding factors* (smoking status, steatosis staging, BMI variations, physical exercise, adherence to antidiabetic therapy) are urgently needed to establish the persistence of such an amelioration.
- It is likely that **subgroups of patients will benefit** from viral eradication in the long term as regards glycometabolic issues.

2) Does HCV Clearance with DAAs Lead to Significant Improvement of Glycometabolic Control in Patients *with Diabetes*? If so, is This Control Maintained over the Long Term?

- It is also likely that patients with **advanced cirrhosis and/or a long duration of diabetic disease**, will ***not*** **experience lasting benefits** *from viral clearance* and any improvement in glycometabolic control will have to be based on lifestyle and adherence to antidiabetic therapy.
  - "This observation suggests a **point of no return** where the impact of viral eradication on the outcome of diabetic disease is minimal or irrelevant;
    - therefore, it is *extremely important to quickly identify HCV-positive diabetic patients* in order to start antiviral therapy without delay
      - to stop fibrotic progression, on the one hand, and
      - to reduce the risk of the occurrence of extrahepatic complications related to diabetes on the other."

3) Does SVR-related glycometabolic improvement induce de-escalation/withdrawal of antidiabetic therapy?

- Conclusions: Most of the studies reporting improvements in glycol-metabolic control ***showed reduction/suspension of antidiabetic therapy*** in a ***significant minority*** of patients.
- It has been suggested that **diabetic patients with DAA-induced SVR** should be ***carefully monitored regarding their glycometabolic profile in order to avoid hypoglycemic episodes***.
  - However, due to the heterogeneity and incompleteness of the data and brief follow up the review was unable to
    - assess the characteristics of the patients who obtained this reduction/suspension
    - identify a particular class of drugs particularly sensitive to this variation.
    - determine whether this modification was maintained over the long term.
  - Future work will need to precisely evaluate antidiabetic therapy modification in more depth as it represents a clinically meaningful endpoint.

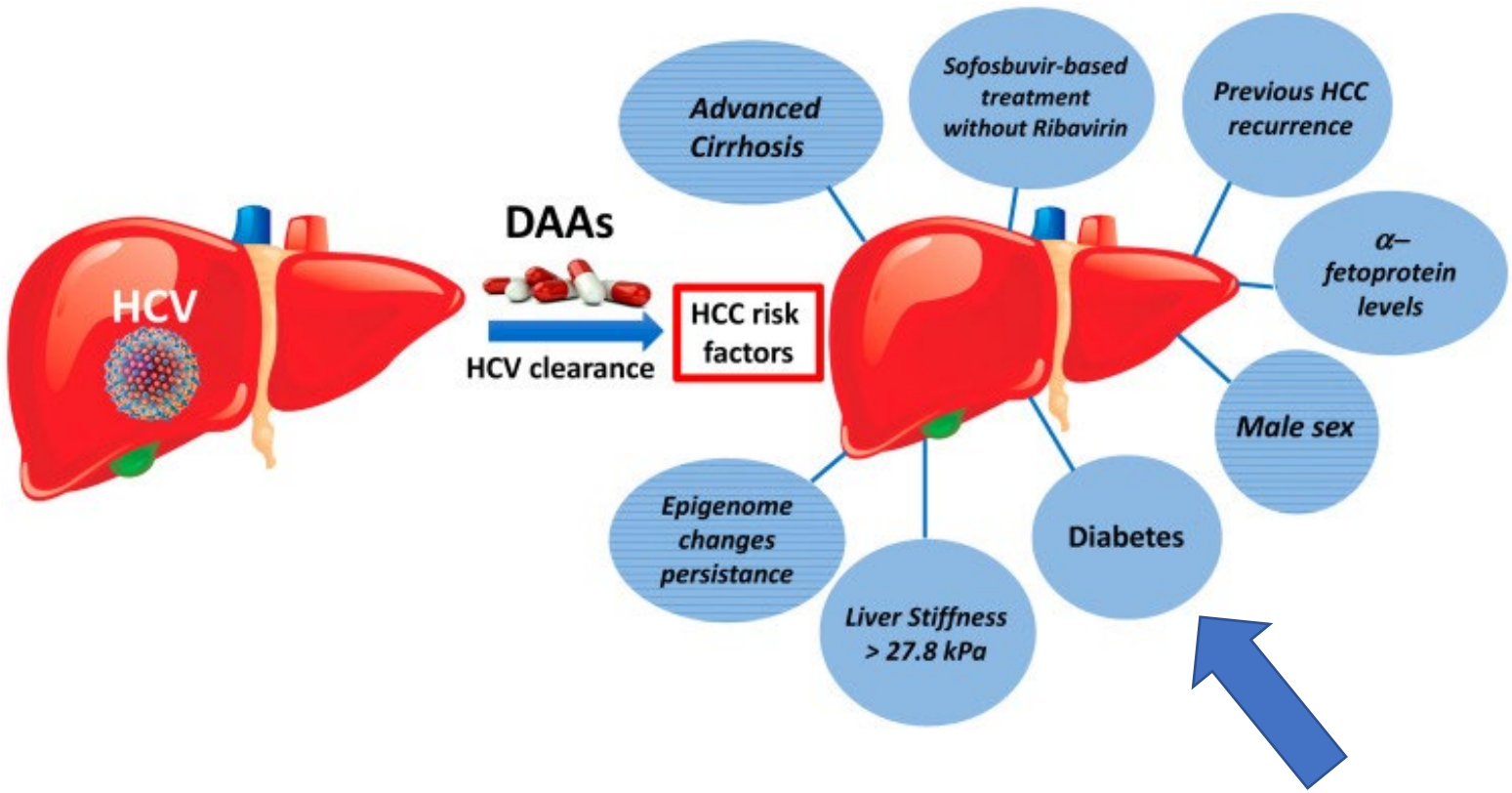
4) Do DAA-Induced Glycemic Changes Determine a Significant Clinical Impact on the *Outcome of Diabetes and its Complications*?

- Studies have shown that SVR from treatment with INF or DAAs result in **significant reductions in mortality (from any cause)** and in the incidence of hepatocellular carcinoma (HCC) in treated patients compared to untreated
  - It is *unclear* whether **the reduction in complications of diabetic disease** observed after viral eradication is mainly due to *glycometabolic improvement* or to the *direct beneficial effect of viral clearance* on extrahepatic sites. (see list of extrahepatic manifestations of HCV)
    - the improvement of extrahepatic manifestations of HCV infection (in particular, ***cardiovasculopathies and nephropathies***) coinciding with the most frequent complications of diabetic disease may improve after viral clearance due not only to glycometabolic control amelioration, but also to other mechanisms yet to be established.
      - In the case of **nephropathy**, it is likely that HCV eradication may lead to an improvement in ***vasculitis–cryoglobulinemic damage***;
      - The beneficial effect of viral eradication on **cardiovascular diseases** may be derived from the disappearance of the ***systemic inflammatory*** status, the ***decrease in TNF- and IL-6 levels***, and the ***increase in adiponectin levels***.

5) What is the Clinical Impact of DAA-Induced SVR on The Incidence of HCC in Diabetic Patients?

- Unclear from their review – Conclusion was that ***most likely the magnitude of risk reduction in HCC incidence found among diabetic patients with SVR is probably comparable to that observed in nondiabetics***;
  - However, because of discrepancy in the data between the IFN period (showing reduced risk of HCC w SVR) and the DAA period (no reduced risk), further consideration is required.
  - Much evidence suggests that ***diabetes*** is an *independent predictor of HCC*, despite viral eradication obtained by IFN-based therapies (less so with DAA therapy)
    - One study showed that maintaining HbA1c levels <7.0% during follow-up significantly reduced the onset of HCC in diabetic patients with IFN-induced SVR.
    - Studies suggest a ***protective*** action of **metformin** therapy against HCC compared to other antidiabetic treatments (a significant increase in the survival of DM patients with cirrhosis of any etiology who were continued on metformin)
  - Recent studies show evidence of **HCV-induced epigenetic** changes associated with HCC risk. This viral epigenetic signature in the host genome is ***often irreversible***, especially for those patients with advanced liver fibrosis (indicates ongoing risk of HCC)

Risk factors of occurrence or recurrence of HCC after HCV clearance by DAAs treatment



Dr. Mera – based on fibrosis score of F3 or F4 *before* starting treatment –
Screen with Alpha-fetoprotein and US every 6 months

Summary

- Chronic HCV with or without cirrhosis can lead to or worsen diabetes (IR, glycemic status, outcomes)
- Achieving SVR with treatment can prevent or improve diabetes (glycemic status) in some subgroups of patients
  - Less likely with longstanding HCV and more extensive fibrosis
  - This may result in need for less medication for diabetes management
    - Close monitoring suggested for those on diabetes medications (especially insulin & sulfonylureas)
  - The duration of the improved glycemia is uncertain (more data needed)
- Achieving SVR from HCV can reduce complications/improve outcomes for people with diabetes
  - Unclear if this is due to improved glycemia and/or reduced extra-hepatic effects of HCV due to viral clearance
- Ongoing surveillance for Hepatocellular Carcinoma (HCC) still required in many patients

Outcomes of hepatitis C treatment on type 2 diabetes. How different is managing type 2 diabetes before and after hepatitis elimination.

Post-test

Achieving sustained viral remission (SVR) with treatment of HCV

A. Often results in weight gain that can worsen diabetes control
B. Can worsen insulin resistance (IR) and hyperglycemia
C. Can reduce insulin resistance and hyperglycemia
D. Is most effective in those with more extensive hepatic fibrosis

Resources:

- HCV ECHO link: https://www.indiancountryecho.org/program/hepatitis-c/
- SUD ECHO link: https://www.indiancountryecho.org/program/substance-use-disorder/
- UCSF consult service: https://nccc.ucsf.edu/clinician-consultation/hepatitis-c-management/

- https://www.indiancountryecho.org/wp-content/uploads/2021/10/Hep-C-DAA-and-Viral-Clearance-for-patients-with-Diabetes.pdf

Summary from didactic on Hepatogenic Diabetes

- Diabetes increases fibrosis in liver disease →cirrhosis
- Diabetes complicates cirrhosis→ increased morbidity (risk of cirrhosis complications/decompensated cirrhosis) & mortality
  - Increased risk of Hepatocellular Carcinoma (HCC)
- Cirrhosis can cause abnormal glucose metabolism
  - Hepatogenous diabetes
- A1c is unreliable in cirrhosis (tends to be falsely low due to hypersplenism)
  - ? Role of CGM to help determine glycemic status
- Coexisting cirrhosis requires extra consideration of medication options
  - Metformin safe & increases survival
  - SGLT2i – potential for safe Rx of both ascites & glycemia
  - GLP1RA meds do not require dose reduction
  - Avoid insulin secretagogues
  - Variable insulin requirements – increased hypoglycemic risk

Cancers (Basel). 2020 Jun; 12(6): 1351.
Published online 2020 May 26. doi: 10.3390/cancers12061351
PMCID: PMC7352473
PMID: 32466400
Risk of Hepatocellular Carcinoma after HCV Clearance by Direct-Acting Antivirals Treatment Predictive Factors and Role of Epigenetics
Luca Rinaldi, et al

- Several long-term studies in HCV patients treated with IFN-based regimens have documented a reduction in the incidence of HCC by 75% in patients with SVR and a residual risk of the development of HCC mainly associated with some comorbidities such as metabolic syndrome and diabetes mellitus

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- HCC still represents a serious complication of cirrhosis with a significant mortality rate. In most of the studies reviewed, SVR by DAAs in HCV patients does not appear to have an impact on the occurrence and recurrence rate of HCC in the short-term post-viral clearance, suggesting **that careful surveillance of HCC in patients with cirrhosis should be mandatory.**
  - On the other hand, studies conducted on large numbers of HCV patients treated with DAAs showed a reduction in risk of development of HCC in the medium to long term. Comparative studies between DAAs regimen and IFN-based therapies did not provide solid data for the many differences in the population compared, however, treatment with DAAs does not appear to be less effective than IFN-based regimens in reducing the incidence of HCC.
- The underlying mechanisms of HCC occurrence despite a viral clearance are presently unknown, with no clear evidence supporting a tumorigenic role of DAAs, which remains a controversial hypothesis that must be necessarily verified by ad hoc studies. Moreover, the epigenetic modulation of HCV virus in host cells should be considered, according to emerging data of recent studies.
- Follow-up strategies must reflect these uncertainties, so **careful ultrasound monitoring of cirrhotic patients** is a convincing measure to be taken after HCV clearance by DAAs.