Diabetes & Hepatitis C Virus Infection

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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 – Relationships of Diabetes & Liver Disease

- Diabetes increases fibrosis in liver disease →cirrhosis
- Diabetes complicates cirrhosis→ increased morbidity (risk of cirrhosis complications/decompensated cirrhosis) & mortality (i.e., worsens prognosis)
  - Increased risk of Hepatocellular Carcinoma (HCC)

- Cirrhosis can cause abnormal glucose metabolism (cirrhosis is diabetogenic)
  - **Hepatogenic diabetes** (The pathophysiological basis of HD seems to involve insulin resistance (IR) and pancreatic β-cell dysfunction.)
    - ~30-40% of patients with cirrhosis have overt diabetes (vs ~15% in gen pop)
    - ~80% of patients with cirrhosis

    with a normal FBS have IGT or diabetes based on oral GTT

Sort of a vicious circle –

Insulin resistance increases steatosis & fibrosis

and

Steatosis & fibrosis increase insulin resistance

Background – HCV Infection & Diabetes

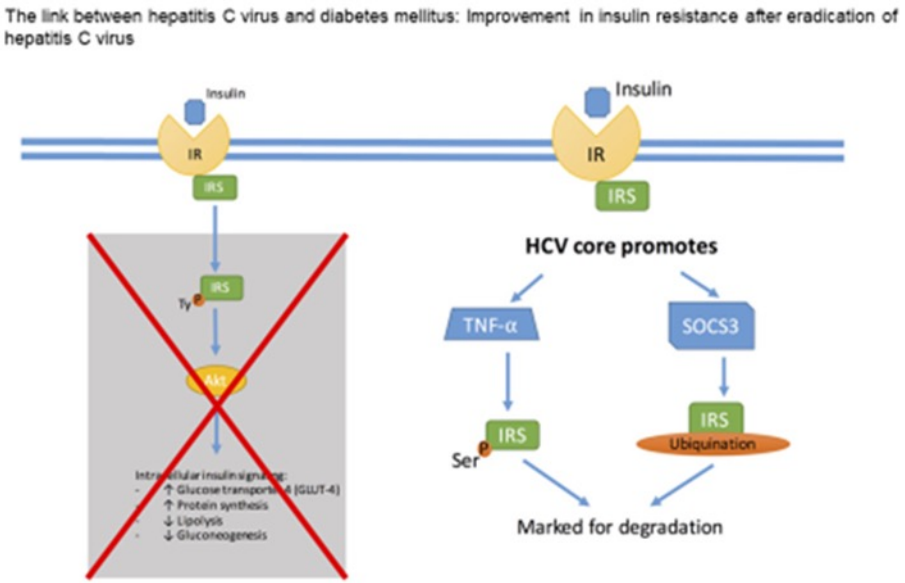
- The prevalence of diabetes is significantly higher among patients with HCV cirrhosis than in patients with cirrhosis due to other etiologies
  - Most studies have noted a 2- to 10-fold increase of T2D in chronic HCV infection compared to other liver diseases
- It is estimated that up to 33% of chronic 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***
- One plausible explanation for this observation is that ***HCV infection,*** *and/or* ***the inflammatory response to infection***, contributes to the development of **Insulin Resistance (IR)** and, as a result, to an increased risk of T2DM

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

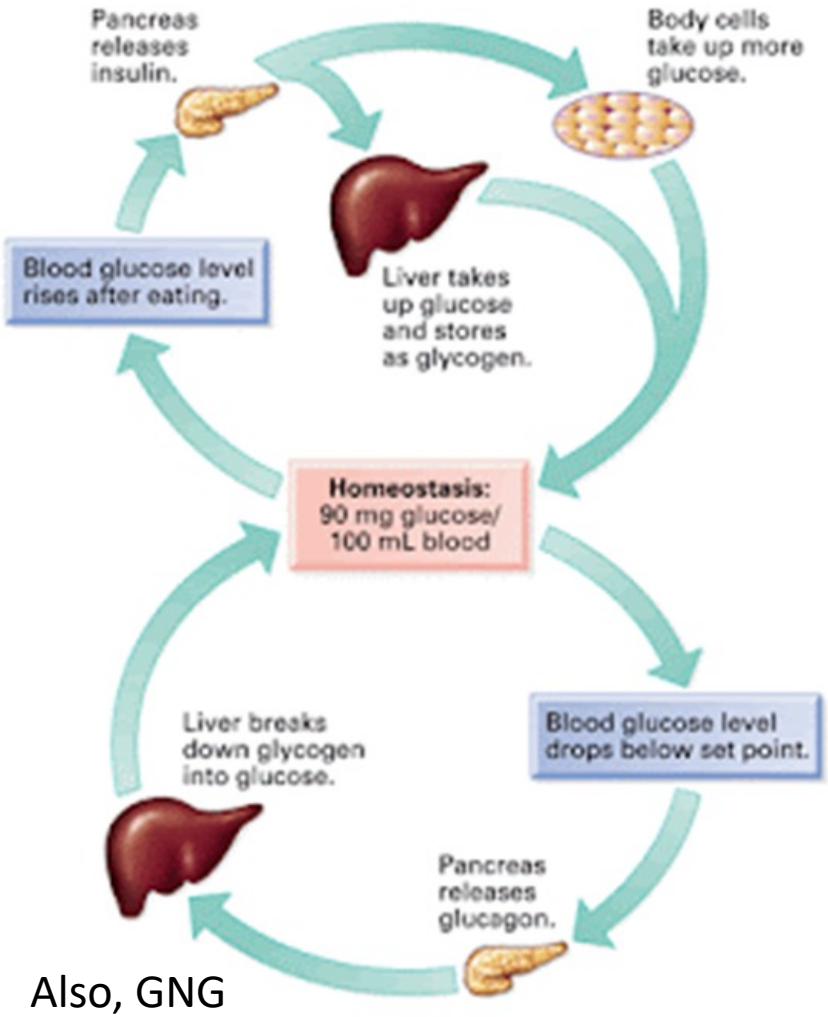
Background – HCV & Insulin Resistance (IR)

- IR makes cells *less responsive* to an established amount of insulin, necessitating larger doses of insulin to produce the same cellular response
- Chronic HCV infection ***impairs intrahepatic insulin signaling pathways*** by increasing the production of TNF-α → degradation of IRS proteins *preventing interaction with the insulin receptor*, resulting in a blockage of glucose uptake at the cellular level (Insulin Resistance)
  - The IRS proteins are a family of cytoplasmic adaptor proteins that transmit signals from the insulin and IGF-1 receptors to elicit a cellular response.



Background – Key Role of Liver in Insulin Action & Glucose Regulation

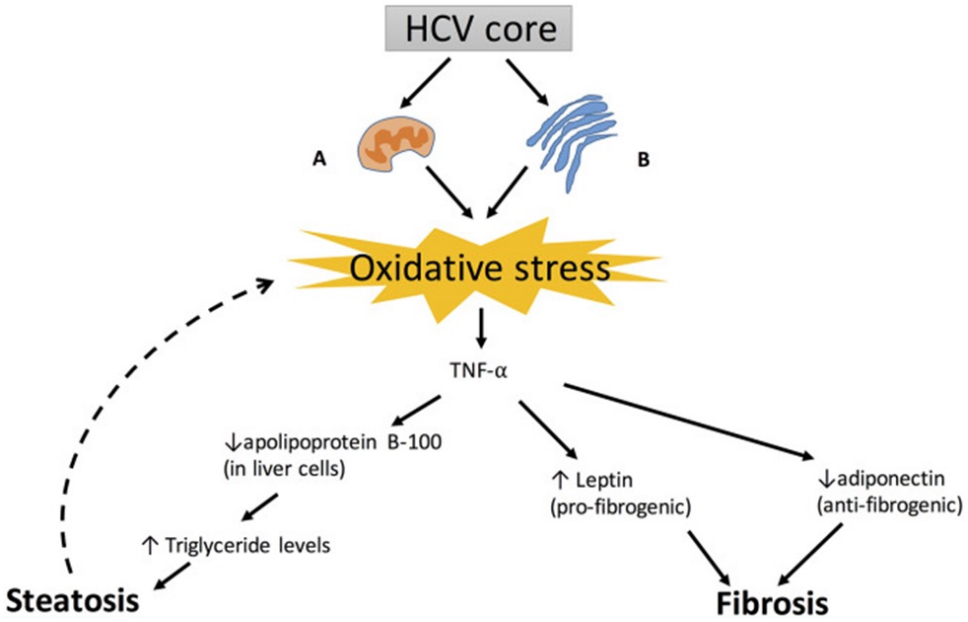
- Insulin is the principal anabolic hormone in the human body.
- The liver plays a key role in maintaining stable glucose concentrations
- Insulin acts on hepatocytes to store glucose as glycogen through glycogenesis or to release glucose from glycogen through glycogenolysis, depending on the body's needs
- Insufficient insulin effect → excessive hepatic glucose output



Also, GNG

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

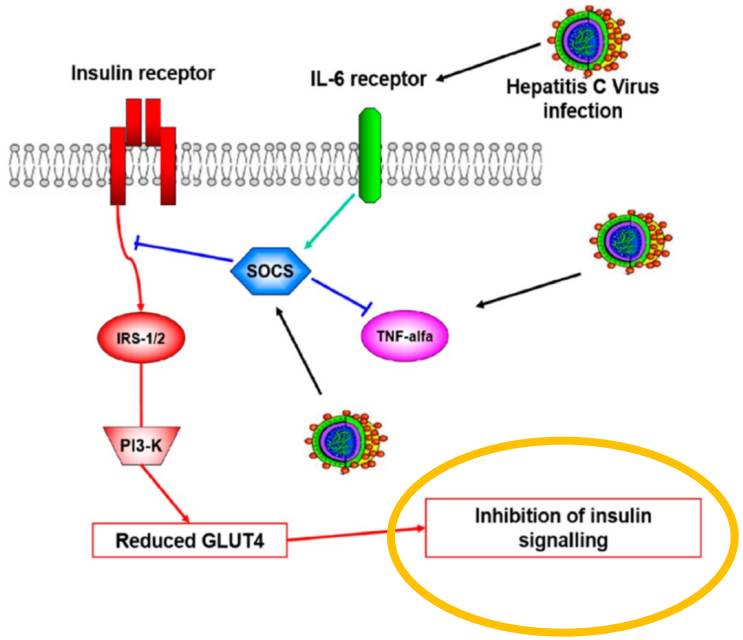


Also increasing IR & CVD risk factors

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 2014, 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

- Caveats:
  - Most of these studies did *not account* for possible ***confounding factors*** (smoking status, steatosis staging, BMI variations, physical exercise, adherence to antidiabetic therapy, etc.) –
  - Whether the beneficial effect is maintained over the *long term* is still undetermined.

More studies are needed ….

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) Most of the studies of patients who were treated with DAAs confirmed a beneficial effect of SVR in *reducing the risk of onset of IR/DM*
- (2) Most studies show an *improvement of glycometabolic control* at the end of therapy or in the immediate post-therapy months in some *subgroups of diabetic patients*.
  - It is 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 patients with diabetes 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."

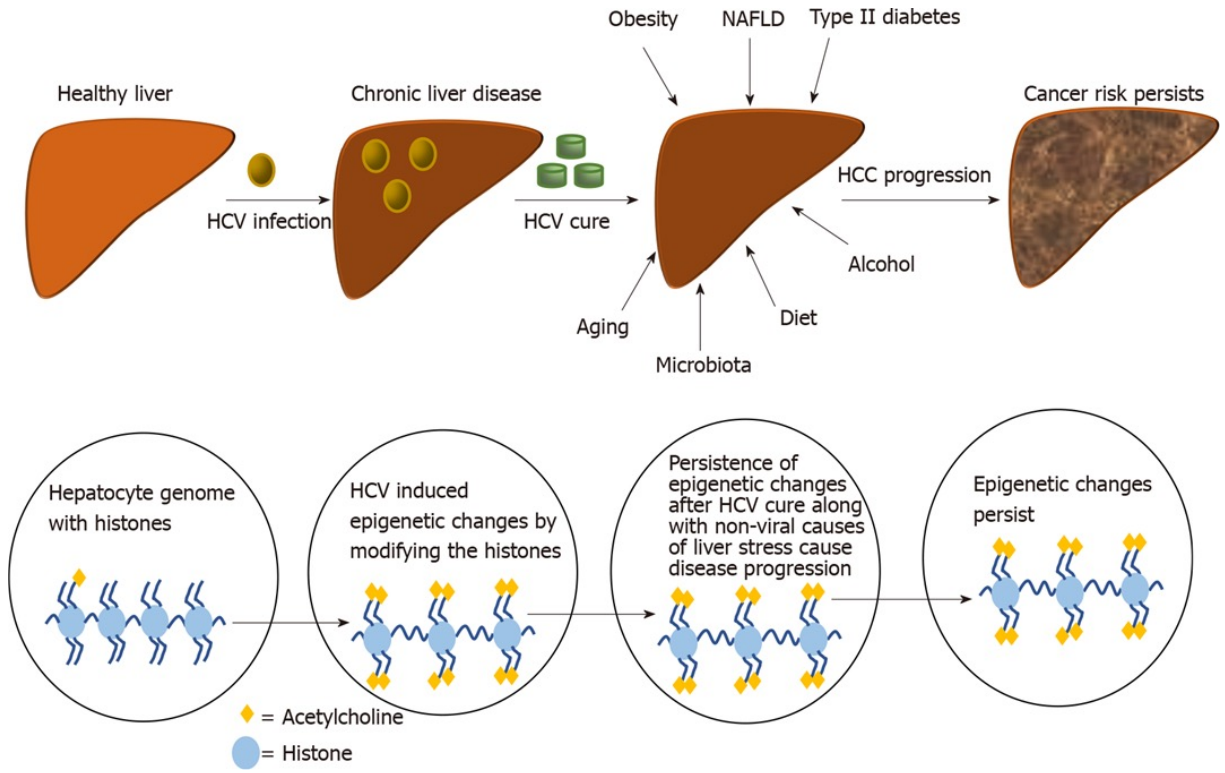
Systematic Review: *The Effect of Viral Clearance Achieved by Direct-Acting Antiviral Agents on Hepatitis C Virus Positive Patients with Type 2 Diabetes Mellitus: A Word of Caution after the Initial Enthusiasm* J of Clin Med Feb 2020

- (3) Most of the studies showed reduction/suspension of antidiabetic therapy in a *significant minority* of patients with SVR.
  - Diabetic patients with DAA-induced SVR should be carefully monitored regarding their glycometabolic profile in order to avoid hypoglycemic episodes (SUs &/or Insulin)
- (4) Studies have shown that SVR from treatment with INF or DAAs result in significant reductions in mortality (from any cause)
  - It is unclear whether the **reduction in complications of diabetes** observed after viral eradication is mainly due to glycometabolic improvement or to the direct beneficial effect of viral clearance on extrahepatic sites.
    - 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(decrease harmful & increase beneficial cytokines)
- (5) The impact of DAA-induced SVR on the incidence of HCC in diabetic patients is *unclear* from this review
  - evidence suggests that diabetes is an independent predictor of HCC, despite viral eradication

Risk of hepatocellular carcinoma after hepatitis C virus cure

World J Gastroenterol. 2022 Jan 7; 28(1): 96–107.

- HCV cure reduces the HCC risk but those with *preexisting cirrhosis* remain at risk
  - Several factors have been associated with progression to HCC after HCV cure including
    - diabetes mellitus
    - underlying non-alcoholic fatty liver disease (steatosis)
    - alcohol consumption



Metformin *and Hepatocellular Carcinoma Risk Reduction in Diabetic Patients with Chronic Hepatitis C: Fact or Fiction?. Viruses. 15(12), 2023 Dec 17.*

Higher risk of HCC in DM patients not taking metformin (~ 11% in one study) than in DM pts taking metformin (2.6%) or non-DM pts (3%) – regardless of Rx (not treated, IFN or DAA) or SVR.

A Meta-Analysis: The Extent of Insulin Resistance in Patients That Cleared Viral Hepatitis C Infection and the Role of Pre-Existent Type 2 Diabetes Mellitus Marian-Sorin Popescu, et al Reports 2022, 5(4), 42

- The meta-analysis showed **that clearance of HCV leads to improvement of IR**, especially in the case of patients with T2DM.
  - The considerable decrease in IR post-SVR may be explained by the decrease in hepatic inflammation that happens after HCV eradication.
- **Insulin sensitivity improves *independently of weight loss*, confirming *HCV-related chronic hepatitis as a separate risk factor* for the development of IR.**
  - ***High BMI significantly decreased the likelihood of IR improvement***. Obesity is a hallmark of metabolic syndrome and has been linked to IR.
  - Patients with HCV who achieve SVR but remain overweight and/or insulin resistant may be at an increased risk of long-term liver and non-liver complications.
    - Therefore, in these patients, IR should be managed by dietary intervention (a combination between calorie restriction and reduction in carbohydrates with high glycemic index) and in selected cases by pharmacological interventions.

https://www.mdpi.com/2571-841X/5/4/42

Hepatitis C Virus Clearance with Glucose Improvement and Factors Affecting the Glucose Control in Chronic Hepatitis C Patients | Scientific Reports (nature.com)

- In conclusion, patients with HCV infection had a higher prevalence of abnormal glycometabolism [that]could be improved after viral eradication.
- Baseline characteristics were Independent risk factors for *less improvement* in glucose metabolism (unimproved glucose after SVR):
  - Older age (>/= 61)
  - Higher viral load (higher baseline HCV RNA >/= 6.55 log IU/ml)
  - Higher glucose
  - Worse liver function (higher TBiL and ALT)

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 & diabetes, more extensive fibrosis or Obesity
  - 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
  - Treatment with metformin may reduce HCC risk

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

EXTRA SLIDES

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) – due to INF not HCV

GLP-1 Receptor Agonists in Non-Alcoholic Fatty Liver Disease: Current Evidence and Future Perspectives Int J Mol Sci. 2023 Jan; 24(2): 1703

- The available evidence on GLP-1 RAs allows us to hypothesize a potential efficacy of this class of drugs in achieving
  - long-term regression of fibrosis
  - a ***reduced incidence/recurrence of HCC*** in patients with NASH.
- These hypotheses need to be verified in dedicated trials.

- GLP-1 RAs have been shown to *improve liver enzymes and hepatic fat accumulation* as well as *promote resolution of steatohepatitis in patients with NAFLD.*
  - The reduction in body weight and the improved glycemic control resulting from these drugs are certainly crucial factors in the improvement of NAFLD parameters. [a weight loss of ≥7–10% seems to significantly improve the hepatic necro-inflammation and fibrosis.]
  - It is not known whether these effects can also be attributed to a *direct action* of GLP-1 RAs

Good explanation for Patients

- https://www.webmd.com/hepatitis/hepatitis-c-diabetes-link

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

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https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/cld.694 Clinical Liver Disease
The link between hepatitis C virus and diabetes mellitus: Improvement in insulin resistance after eradication of hepatitis C virus
Justine Hum M.D., Janice H. Jou M.D., M.H.S.
First published: 06 April 2018 https://doi.org/10.1002/cld.694Citations: 12

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