# Il coinvolgimento del pancreas nella patologia epatica

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# DISCLOSURES

Il dott Stefano Ciardullo dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

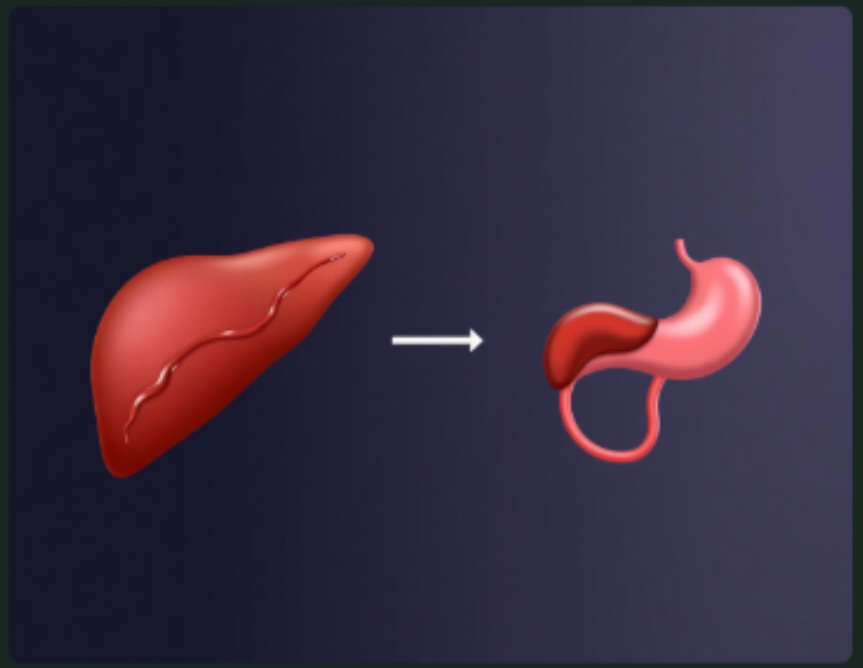
- AstraZeneca
- Boheringer Ingelheim
- Echosens
- Eli Lilly
- Guidotti
- MSD
- Novo Nordisk

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

# Presentation Overview

- Defining Hepatogenous Diabetes (HD) and the Diagnostic Challenge
- Epidemiological Landscape of Diabetes in Cirrhosis
- Pathophysiology: Insulin Resistance vs. B-cell Dysfunction
- Distinct Clinical Features and Prognostic Impact
- The Effect of Orthotopic Liver Transplantation (OLT)
- Conclusions and Future Directions

# Defining Hepatogenous Diabetes



Hepatogenous Diabetes (HD) is defined as a state of impaired glucose regulation directly caused by the loss of liver function secondary to cirrhosis. A critical component of this definition is that the onset of diabetes mellitus (DM) occurs *after* the onset of cirrhosis.

# The Diagnostic and Classification Dilemma

Despite a long-recognized association between cirrhosis and DM, hepatogenous diabetes is not currently considered a separate clinical entity. This is primarily due to the difficulty in distinguishing it from classical Type 2 Diabetes (T2DM).

## The Bidirectional Relationship

- T2DM and metabolic syndrome can cause or accelerate chronic liver diseases like Nonalcoholic Fatty Liver Disease (NAFLD), which can progress to cirrhosis.
- Specific causes of liver disease, such as Hepatitis C Virus (HCV), have direct diabetogenic effects that can precede cirrhosis.
- When cirrhosis and DM coexist, they mutually influence each other's progression and severity, regardless of which appeared first.

# Section I: The Epidemiological Landscape

The prevalence of diabetes mellitus among individuals with cirrhosis is highly variable, with estimates in literature ranging from 20% to 70%. This wide variation is influenced by several key factors.

### Diagnostic Criteria

The use of different tests and cut-off points (e.g., FPG vs. OGTT) drastically alters reported prevalence.

### Stage of Liver Disease

The severity of cirrhosis, often measured by Child-Pugh class, correlates with the prevalence of diabetes.

### Etiology of Liver Disease

The underlying cause of cirrhosis (e.g., alcohol, HCV, NAFLD) affects the risk and nature of associated diabetes.

# The Crucial Role of the Oral Glucose Tolerance Test (OGTT)

Relying solely on Fasting Plasma Glucose (FPG) or Haemoglobin A1c (HbA1c) significantly underestimates the prevalence of glucose metabolism disorders in cirrhotic patients. Many present with normal fasting levels but exhibit significant post-challenge hyperglycemia.

## Diagnosis via FPG / HbAIc

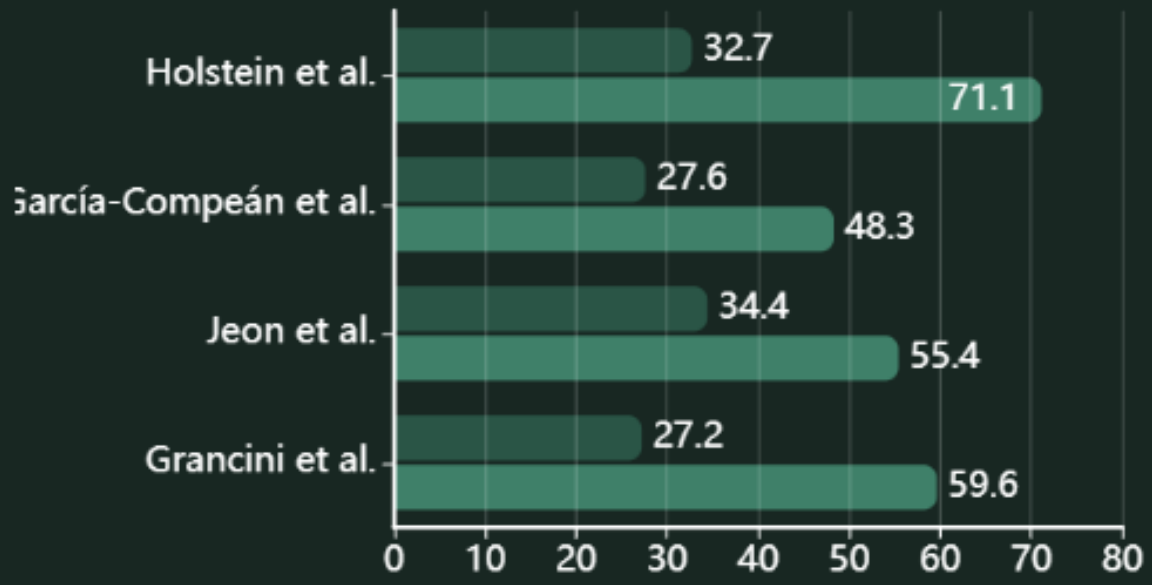
Studies using only these methods report a DM prevalence of approximately 30-40% in cirrhotic cohorts.

## Diagnosis via OGTT

When an OGTT is performed on patients with normal fasting glucose, an additional 35-55% are diagnosed with DM, and 25-40% with Impaired Glucose Tolerance (IGT).

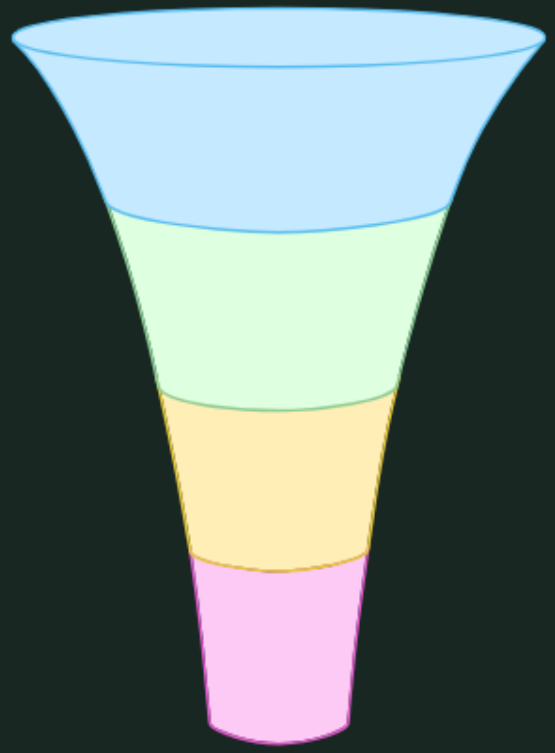
# Prevalence of Glucose Regulation Abnormalities in Cirrhosis

Analysis of multiple studies demonstrates the diagnostic gap between fasting glucose measurements and the more sensitive OGTT. The combined approach reveals that abnormal glucose regulation affects the vast majority of patients.



# Estimating the Prevalence of "True" Hepatogenous Diabetes

A significant portion of DM in cirrhotic patients is pre-existing T2DM. True hepatogenous diabetes is best represented by patients with normal fasting glucose who show an abnormal response to an OGTT. Based on this, it is estimated that the prevalence of true HD in cirrhotic patients is approximately 35-40%.



All Cirrhotic Patients

~60-70% have DM (by FPG+OGTT)

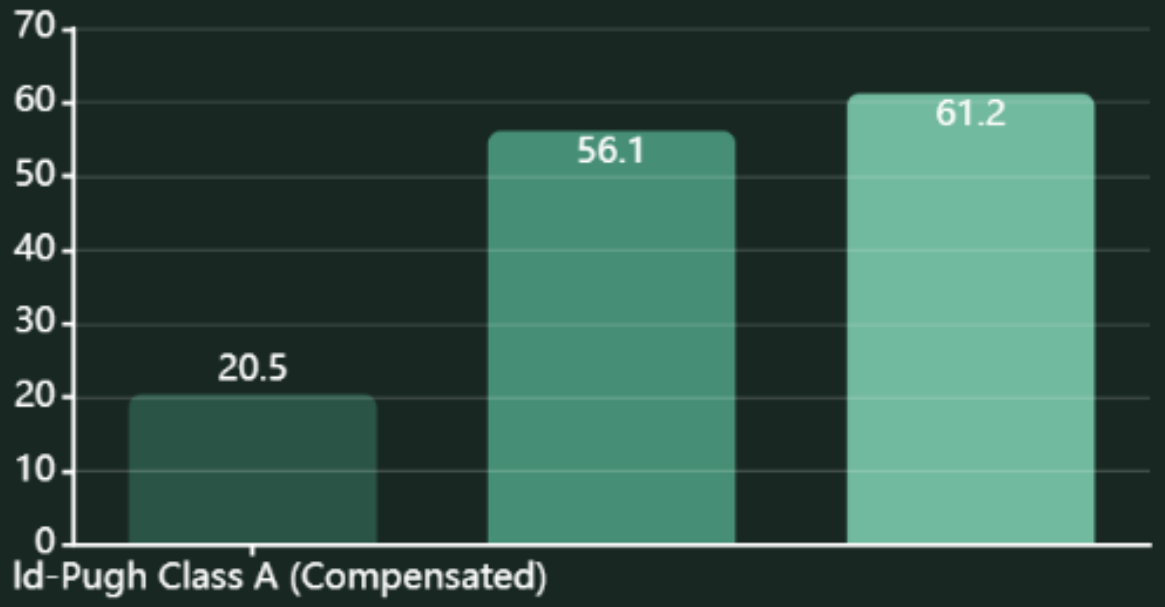
~Half of DM cases are pre-existing T2DM

~35-40% of total cohort have True Hepatogenous Diabetes

# Correlation with Liver Disease Severity

There is a strong correlation between the severity of liver dysfunction and the prevalence of diabetes. As liver function deteriorates, the risk of developing diabetes increases significantly.

## Prevalence by Child-Pugh Classification



# Influence of Liver Disease Etiology

The underlying cause of liver disease significantly impacts diabetes risk through distinct mechanisms.

### Alcoholic Liver Disease & Hemochromatosis

Associated with a higher risk of DM, partly due to direct toxic effects of alcohol and iron on pancreatic β-cells.

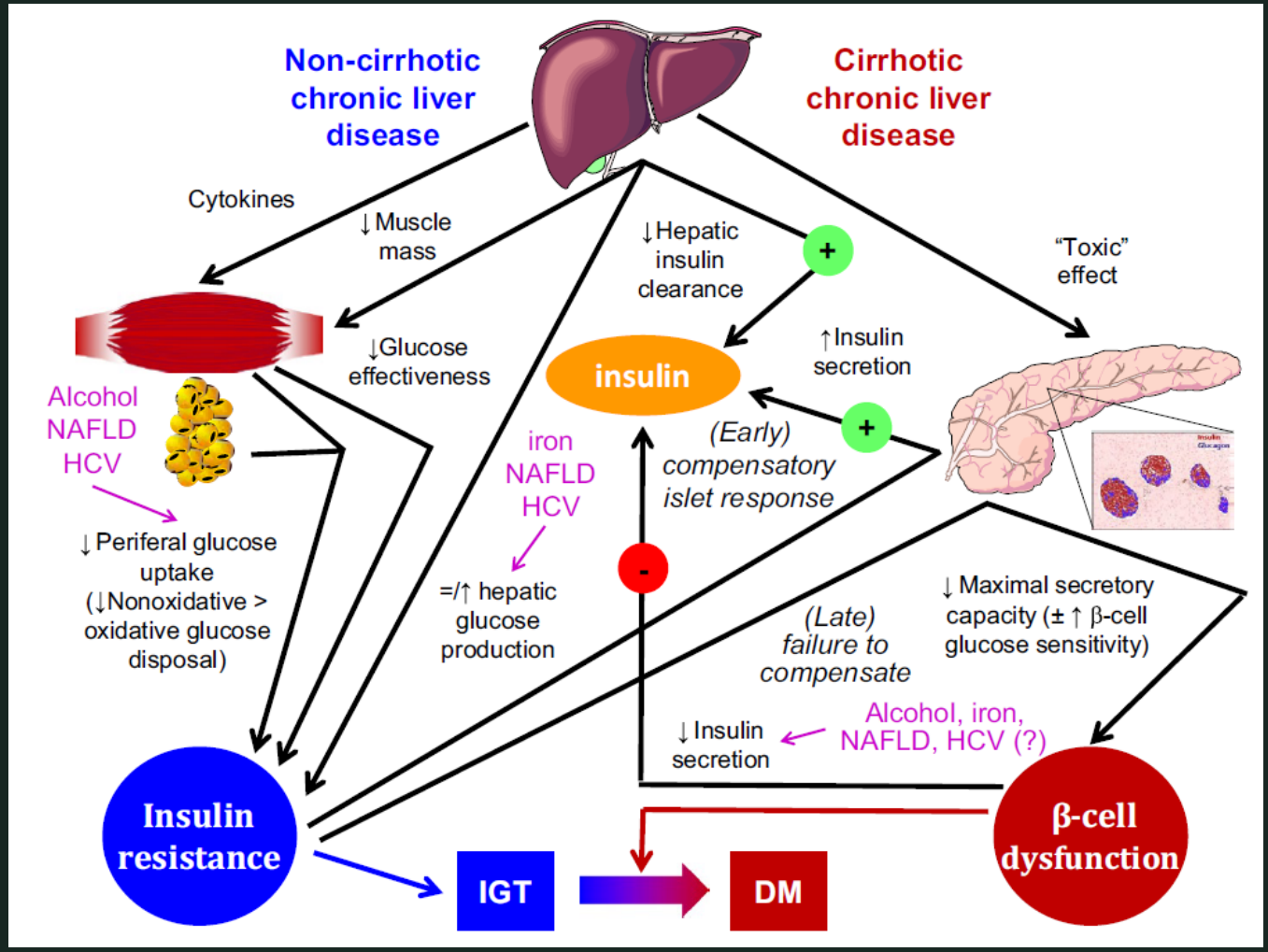
### NAFLD & Metabolic Syndrome

In this context, DM is often the cause rather than the consequence of liver disease, with insulin resistance being a central pathogenic driver for both conditions.

### Hepatitis C Virus (HCV)

HCV has a direct diabetogenic effect, inducing insulin resistance even in pre-cirrhotic stages. However, once cirrhosis develops, the effect of liver dysfunction itself becomes the dominant factor.

# Section 2: Pathophysiology of Hepatogenous Diabetes



# Pathophysiology: Insulin Resistance (IR)

Insulin resistance is a major defect present even in the pre-cirrhotic stages of chronic liver disease. It is characterized by:

- Reduced whole-body glucose uptake, primarily in muscle and adipose tissue.
- Impaired non-oxidative glucose disposal (glycogen synthesis).
- Unaffected or even reduced hepatic glucose production in early cirrhosis, which increases as overt DM develops.
- Decreased glucose effectiveness, partly due to cirrhosis-induced sarcopenia (loss of muscle mass).

# The Enigma of Hyperinsulinemia

A hallmark of hepatogenous diabetes is significantly higher serum insulin levels compared to T2DM. The cause of this hyperinsulinemia is debated, representing a 'chicken or egg' scenario.

## Theory I: Reduced Clearance

Hyperinsulinemia is a consequence of reduced hepatic clearance of insulin due to hepatocyte dysfunction and portal-systemic shunting. Elevated insulin levels then down-regulate insulin receptors, causing resistance.

## Theory 2: Adaptive Hypersecretion

Insulin resistance is the primary defect, driven by disease-specific factors. The pancreas compensates by increasing insulin secretion, leading to hyperinsulinemia. Reduced clearance is a later event that aggravates the condition.

# Cause-Specific Mechanisms of Insulin Resistance: NAFLD

In Nonalcoholic Fatty Liver Disease (NAFLD), insulin resistance is driven by a complex interplay of metabolic dysfunctions.

1 **Adipose Tissue Dysfunction**

Obesity-related inflammation leads to altered adipokine secretion, increased pro-inflammatory cytokines (like TNF-α), and excess free fatty acid (FFA) release, all of which impair insulin signaling.

2 **Hepatic Steatosis (Fatty Liver)**

An influx of FFAs and increased hepatic fat synthesis lead to the accumulation of lipid intermediates in the liver, which directly interfere with insulin signaling pathways.

3 **Reduced Incretin Effect**

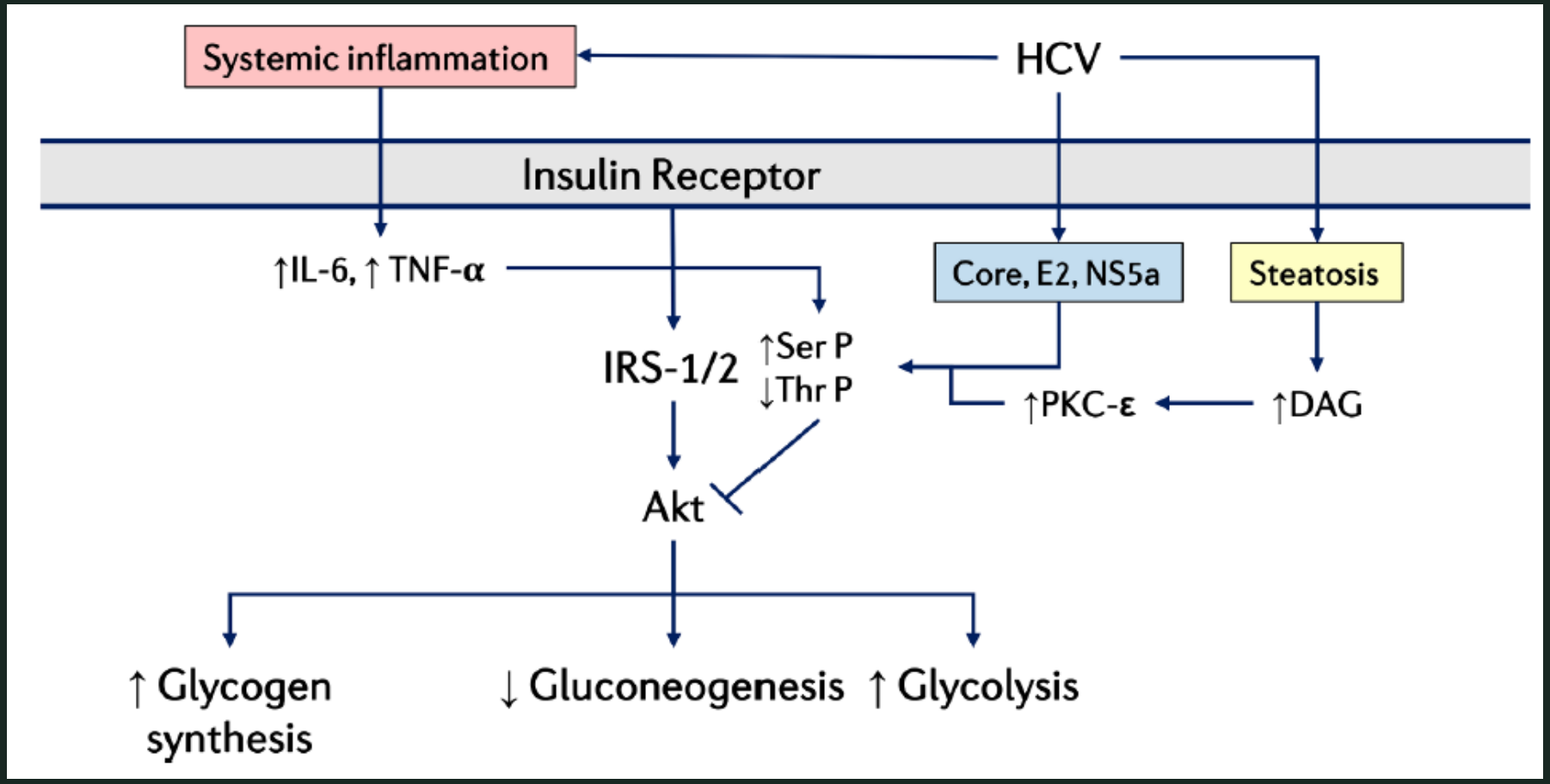
NAFLD is associated with a blunted response to incretin hormones (like GLP-1), impairing glucose-dependent insulin secretion and other beneficial metabolic effects of these hormones.

# Cause-Specific Mechanisms of Insulin Resistance: HCV

Hepatitis C Virus (HCV) directly induces insulin resistance, particularly in the liver, through multiple molecular mechanisms.

## Key Viral Interference Pathways:

- **Activation of Inflammatory Pathways:** HCV infection increases levels of TNF-α, which disrupts insulin signaling.
- **Direct Interference with Insulin Signaling:** HCV proteins directly cause the inactivation and degradation of key signaling molecules like Insulin Receptor Substrate 1 and 2 (IRS-1/2).
- **Promotion of Steatosis:** HCV stimulates fat synthesis and impairs fat breakdown/export from the liver, leading to steatosis which itself contributes to insulin resistance.




Ciardullo S et al. Diabetes Res Clin Pract 2022 May:187:109870

# Pathophysiology: β-Cell Dysfunction

While insulin resistance sets the stage, the deterioration of pancreatic β-cell function is the crucial event that precipitates the transition to overt diabetes. The β-cells can no longer secrete enough insulin to compensate for the resistance.

## Etiology-Specific Damage

- **Alcohol:** Direct toxic effects on β-cells.
- **Iron (Hemochromatosis):** Accumulation and damage to β-cells.
- **NAFLD:** Lipotoxicity from excess free fatty acids impairs β-cell function.
- **HCV:** May cause direct or indirect (auto-immune) damage, though this is debated.

## The Independent Effect of Cirrhosis

Crucially, recent evidence shows that worsening liver function (i.e., decompensation) has a direct, detrimental effect on β-cell insulin secretion, independent of the underlying cause or the degree of insulin resistance.

# The "Toxic" Effect of the Failing Liver on β-Cells

The progression from compensated to decompensated cirrhosis appears to release or fail to clear substances that are toxic to pancreatic β-cells. This intrinsic effect of liver failure is a cornerstone of the argument for HD as a distinct entity. Several potential mediators are being investigated.

### AGEs / ALEs

Advanced Glycation/Lipoxidation Endproducts, which are normally cleared by the liver, accumulate in cirrhosis and are known to impair β-cell function.

### Hypoxia-Inducible Factors (HIFs)

Chronic hypoxia is common in severe cirrhosis. The activation of HIFs, which mediate the cellular response to low oxygen, has been implicated in β-cell dysfunction.

### Betatrophin

A hormone produced by the liver that influences β-cell proliferation. Its levels are altered in cirrhosis, suggesting a disrupted cross-talk between the liver and pancreas.

# Distinguishing Clinical Features: HD vs. T2DM

| Feature | Hepatogenous Diabetes (HD) | Type 2 Diabetes (T2DM) in CLD |
|---|---|---|
| Onset | Typically *after* cirrhosis diagnosis | Typically *before* cirrhosis diagnosis |
| Presentation | Often subclinical: normal FPG/HbA1c, requires OGTT for diagnosis | Overt DM: elevated FPG and/or HbA1c |
| Traditional Risk Factors | Less frequently present (e.g., family history, obesity) | More frequently present |
| Hypoglycemia Risk | Higher, due to impaired hepatic glucose production | Lower (relative to HD) |
| Diabetic Complications | Lower incidence of micro/macrovascular complications | Higher incidence (typical T2DM profile) |
| Effect of Liver Transplant | Should theoretically reverse or ameliorate | Persists after transplant |

# Increased Clinical Risks in Hepatogenous Diabetes

The unique pathophysiology of HD, tied to liver failure, increases the risk of specific adverse events during management.

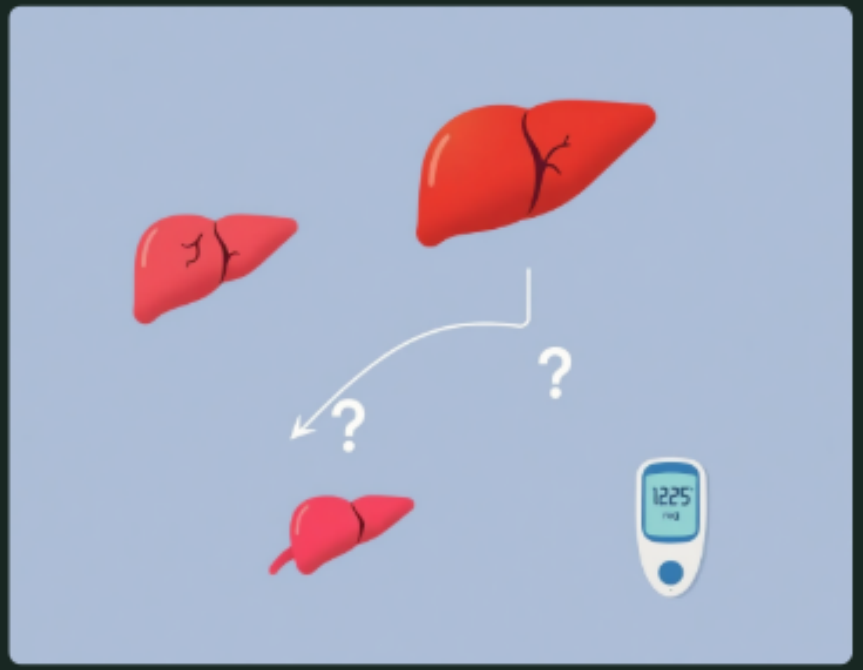
## Higher Risk of Hypoglycemia

The failing liver has an impaired ability to mount a counter-regulatory response (i.e., produce glucose) during periods of low blood sugar. This makes patients highly susceptible to hypoglycemia, especially when treated with insulin or insulin secretagogues.

## Higher Risk of Lactic Acidosis

The liver is the primary site for lactate clearance. In severe cirrhosis, impaired lactate metabolism increases the risk of metformin-associated lactic acidosis (MALA), a rare but serious complication.

# Section 5: The Effect of Orthotopic Liver Transplant (OLT)



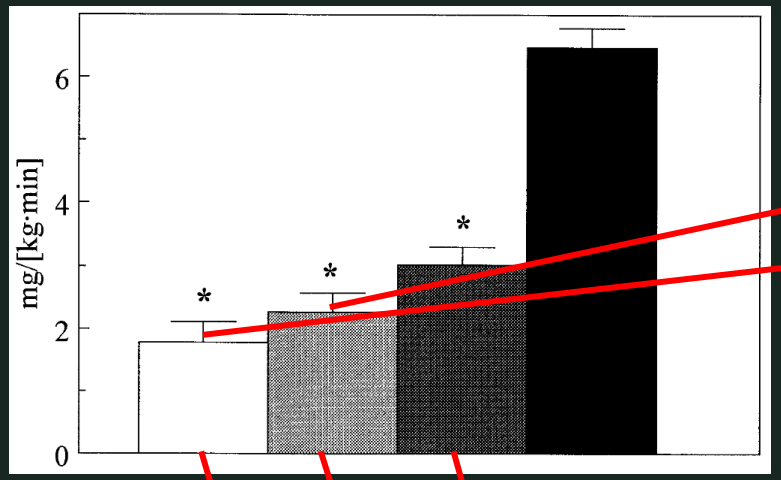

By definition, true hepatogenous diabetes should reverse with the restoration of liver function via transplantation. However, the clinical reality is more complex.

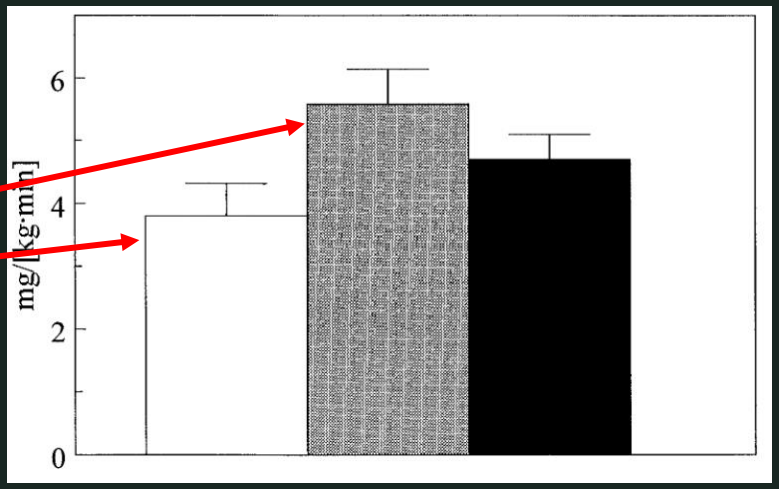
Pre-Tx

Post-Tx (2 years)

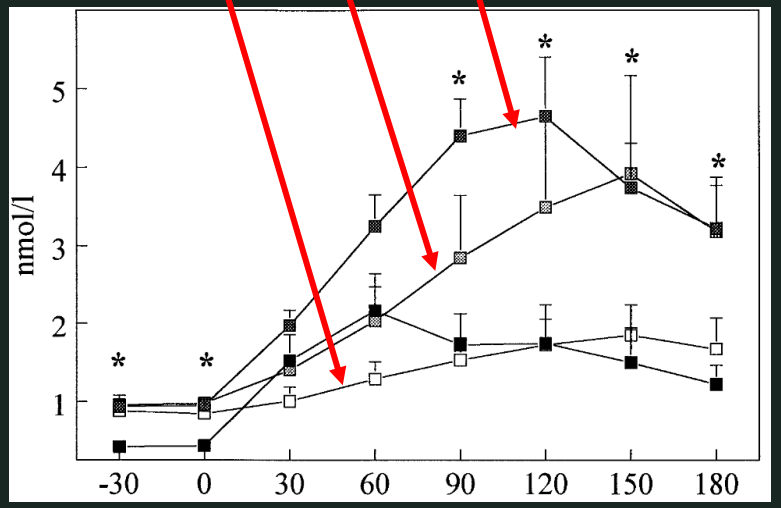
Insulin sensitivity (Clamp)

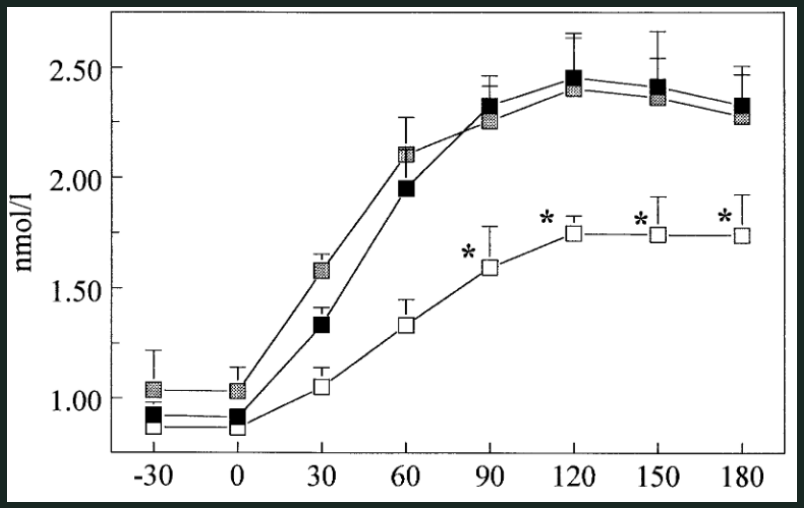
CIR-D noncured patient (□), CIR-D cured patients (▒), CIR patients (▒), and normals (■)




C peptide (OGTT)



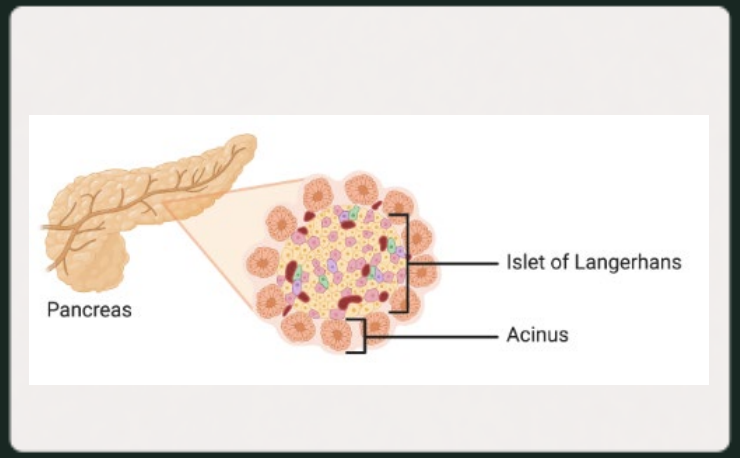




Perseghin G et al. Hepatology 2000 Mar;31(3):694 703

# Factors Contributing to Post-Transplant Diabetes

Even with a new, functional liver, several factors work against the normalization of glucose metabolism after transplantation.

**Immunosuppressant Drugs**




**Pre-existing β-Cell Damage**


**Lifestyle Changes**

# Final Thoughts and Call to Action

Hepatogenous diabetes is an underdiagnosed and poorly understood condition with profound prognostic significance. It is time for the clinical and research communities to:

- Acknowledge HD as a distinct clinical entity separate from T2DM.
- Implement routine OGTT screening in all patients with cirrhosis.
- Conduct further research to identify the specific molecular 'toxins' mediating β-cell damage.
- Design clinical trials for therapies specifically targeting β-cell preservation in this population.
- Evaluate the impact of earlier OLT on long-term metabolic health.