Diabetes ECHO
Diabetes & Cirrhosis

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69-year-old male with T2DM & Cirrhosis

- s/p TIA, Stroke, MI, Cr 0.8, eGFR 90, cataracts
- Low IQ but no cognitive impairment on neuro-psych testing
  - Occasionally wonders off
- BMI 36; dc tobacco 2015, dc Alcohol 2017
- Current diabetes meds:
  - **Glargine insulin** 40u QD
  - **Dapagliflozin** 10 mg QD
  - **Metformin** 1000 mg QD
  - **A1c 9.1%** 1/30/20 – **Semaglutide** 0.5 mg weekly added
  - Freestyle Libre – average glucose 153 as of April 2020

- What do you know about diabetes & cirrhosis?
- What meds are safe? What meds might be advantageous?

T2DM is risk factor for liver fibrosis

- **Type 2 diabetes** is a ***risk factor for liver fibrosis development and progression***.
  - Type 2 diabetes is associated with a 2 to 2.5-fold increased risk of cirrhosis development, and of death from chronic liver diseases
    - mainly attributable to non-alcoholic fatty liver diseases (NAFLD).
  - Diabetes mellitus is an independent predictor of cirrhosis in patients with chronic hepatitis B and chronic hepatitis C.

People with diabetes have an increased risk of developing cirrhosis with any liver disease

Diabetes & Cirrhosis

- Diabetes is an independent factor for ***poor prognosis*** in patients with cirrhosis
  - the **risk of death** from chronic liver diseases is increased in patients with type 2 diabetes mellitus
  - diabetes is associated with the occurrence of major ***complications of cirrhosis*** including
    - ascites
    - renal dysfunction,
    - hepatic encephalopathy
    - bacterial infections
    - increased risk of hepatocellular carcinoma in patients with chronic liver diseases.

Diabetes complicates cirrhosis

- Diabetes is associated with the development of **ascites**, independent of MELD score in patients with hepatitis C-related cirrhosis
  - Diabetes is **associated with refractory ascites** in cirrhosis
- Pre-existing diabetes was significantly associated with an increased incidence of **Hepato-Cellular Carcinoma (HCC)** (relative risk 1.87) and **HCC-specific mortality** (relative risk 1.88)
- Diabetes mellitus and cirrhosis are two conditions that ***predispose*** to **bacterial infections**
  - **mortality** is **four-fold higher** in infected patients with cirrhosis
- Association between diabetes and **hepatic encephalopathy** has been shown in several studies

Hepatic Encephalopathy

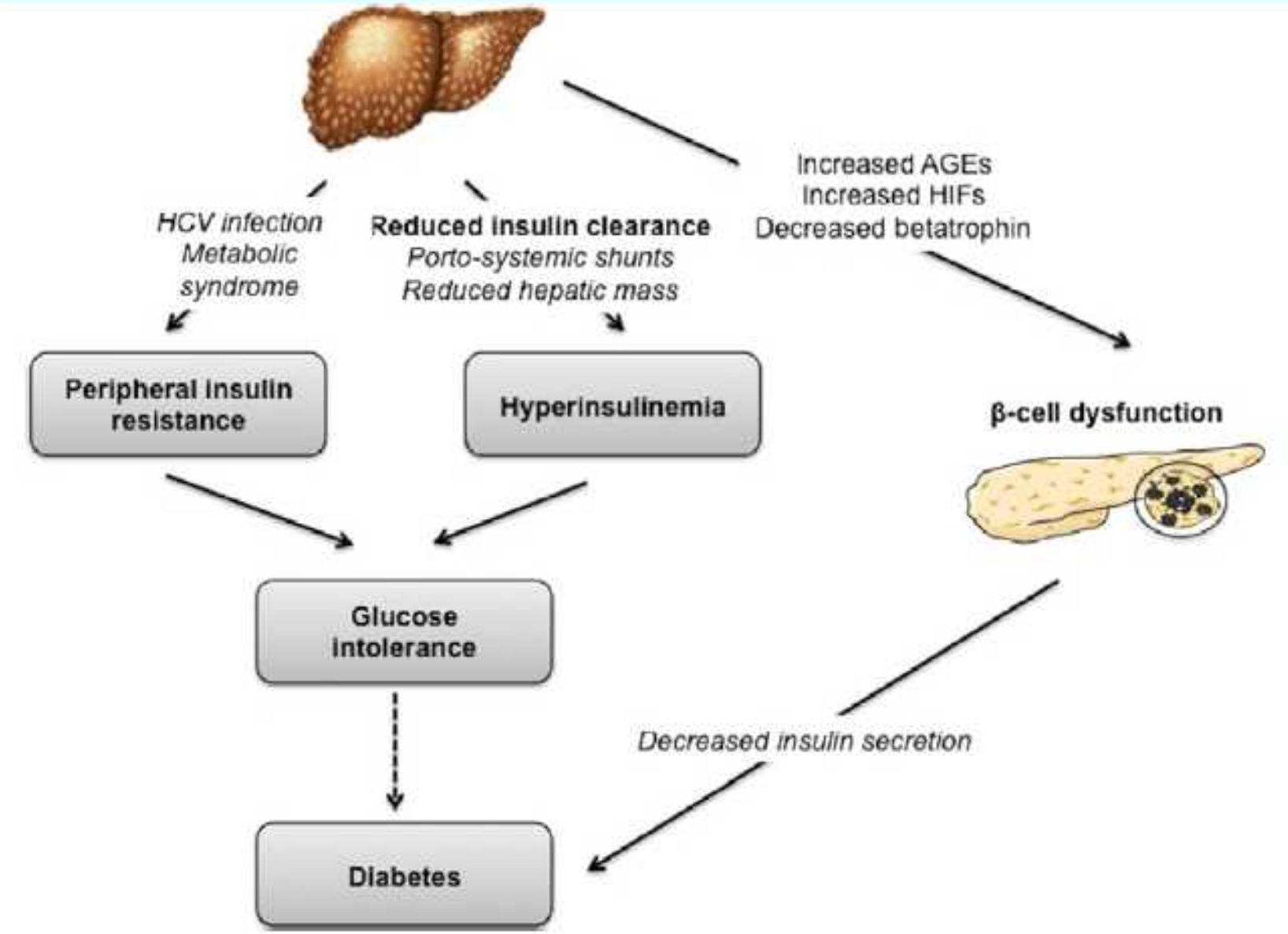
- Several mechanisms by which **diabetes** could theoretically ***promote hepatic encephalopathy*** have been investigated.
  - First, diabetes could *increase ammonia production* by enhancing small intestine glutaminase type K
  - Second, the *inflammatory state* associated with insulin resistance and type 2 diabetes could act synergistically with cirrhosis and endotoxemia associated with encephalopathy
  - Third, intestine motility impairment in diabetic patients as a part of autonomic neuropathy, could promote small intestine bacterial overgrowth
- **Metformin** which reduces glutaminase activity *in vitro* has been shown to ***decrease the incidence of hepatic encephalopathy in patients with cirrhosis***
- **Acarbose,** in patients with cirrhosis and concurrent diabetes significantly ***reduced ammonia blood leve***ls, and improved psychometric tests for minimal hepatic encephalopathy

Cirrhosis as cause of abnormal glucose metabolism

- In patients with cirrhosis
  - ~30% have normal glucose tolerance
  - 30–50% have impaired glucose tolerance
  - up to 30% have overt diabetes (Mayo: 37%)
    - much higher than in the general population, where the prevalence of glucose intolerance is around 15% and that of diabetes is 8%

Hepatogenous Diabetes

Hepatogenous Diabetes



Hepatogenous Diabetes

- Diabetes is more frequent in patients with hepatitis C-related cirrhosis or alcohol-related cirrhosis than in patients with biliary cirrhosis

People with ESLD/ cirrhosis are more likely to develop diabetes due to the liver disease

Diagnosis of Diabetes in Cirrhosis

- Diagnosis of diabetes in patients with cirrhosis may not be easy.
- In early stage - *fasting serum glucose levels is normal* in 23% of the patients with **overt diabetes**:
  - thus, an **oral glucose tolerance test is needed** to detect the impairment of glucose metabolism.
- Discrimination between type 2 diabetes and hepatogenous diabetes is frequently not possible
- Hepatogenous diabetes may have different clinical characteristics from type 2 diabetes
  - only 16% of patients had a family history of diabetes.
  - Only 8% had retinopathy
  - after a mean follow-up of 5 years, no cardiovascular deaths was reported
  - 52% of the patients had died, mainly from complications of cirrhosis
  - liver transplantation by itself can normalize glucose tolerance and insulin sensitivity, supporting the idea that diabetes was related to cirrhosis

A1c in patients with cirrhosis

- Measurement of HbA1c does *not accurately reflect glycemic status in patients with cirrhosis – primarily falsely low results:*
  - 40% of the non-diabetic patients with cirrhosis had HbA1c values *below the normal range* in a non-diabetic reference population
  - patients *with cirrhosis and concurrent diabetes* also had HbA1c values in the non-diabetic reference, namely between 4 and 6%
- ***Shortened erythrocyte (RBC) life span***
  - common in patients with cirrhosis (due to hypersplenism & possible other factors)
  - known to cause low HbA1c values (independent of glycaemia)

Life-style therapy

- The first-line therapy for type 2 diabetes consists of lifestyle changes
  - includes hypocaloric diet and physical exercise.
  - the goal of physical exercise is to increase peripheral insulin sensitivity.
- Unfortunately, in *patients with cirrhosis*, such therapies may be inappropriate or unfeasible.
  - Up to **50 percent of cirrhotic** patients have **malnutrition**, a contraindication to hypocaloric diet.
  - Ascites and edema hamper physical exercise.

Metformin use in Cirrhosis

- A growing number of observational studies suggest that metformin (relative to other glucose-lowering therapies) could be associated with a **reduced risk of cancer** or **cancer mortality**, including **hepatocellular carcinoma**
- Continuation of metformin in patients with newly diagnosed cirrhosis is associated with **a longer survival**
- *Lactic acidosis is rare* despite increasing use of metformin in patients with cirrhosis, suggesting that **metformin is safe in patients with cirrhosis** (those without advanced renal dysfunction)

J Am Pharm Assoc (2003). 2010 May-Jun;50(3):407-10. doi: 10.1331/JAPhA.2010.08090.

Clarifying metformin's role and risks in liver dysfunction.

Conclusion: **Metformin does not appear to cause or exacerbate liver injury**

- Nonalcoholic fatty liver frequently presents with transaminase elevations but should not be considered a contraindication to metformin use.
- Because **metformin is not considered intrinsically hepatotoxic, withholding metformin from patients with abnormal transaminases** or routinely monitoring transaminases before or during metformin treatment **is not supported**

June 2014

T2DM is found in 37% of cirrhotic patients

- Researchers at Mayo Clinic released a new study reversing current thought on the treatment of cirrhotic patients with type 2 diabetes.
  - ***Metformin is usually discontinued once cirrhosis is diagnosed*** because of concerns about an increased risk of adverse effects associated with this treatment in patients with liver impairment.
- The study found that the **continuation of metformin after a cirrhosis diagnosis *improved survival* rates among diabetes** patients.
  - *"Our study suggests that metformin can be used safely in cirrhotic patients. Diabetic patients who take metformin to control their blood sugar levels can continue taking metformin after cirrhosis diagnosis, if there is no specific contradiction,"*

HEPATOLOGY 2014

- Survival of patients who *continued versus discontinued metformin* after cirrhosis diagnosis was compared
- Patients who ***continued metformin had a significantly longer median survival*** than those who discontinued metformin
  - **11.8 vs. 5.6 years** overall, $P < 0.0001$;
  - **11.8 vs. 6.0 years for Child A** patients, $P = 0.006$;
  - **7.7 vs. 3.5 years for Child B/C patients**, $P = 0.04$
  - After adjusting for other variables, continuation of **metformin** remained an ***independent predictor of better survival***, with an HR of 0.43 (95% CI: 0.24-0.78; $P = 0.005$).
- No patients developed metformin-associated lactic acidosis during follow-up.
- *Conclusion*: Continuation of metformin after cirrhosis diagnosis **reduced the risk of death by 57%**.
  - Metformin should therefore be continued in diabetic patients with cirrhosis if there is no specific contraindication

Insulin Secretagogues

- Sulphonylureas and glinides
  - trigger insulin release by the pancreatic beta cells
    - do not modify insulin sensitivity
  - patients with cirrhosis, especially those with *alcohol-related cirrhosis*, may have pancreatic ***beta-islets cell damage*** (less able to respond to Secretagogues)
  - there is an increased risk of **hypoglycemia** with these therapies in patients with cirrhosis
    - Reduced hepatic clearance of insulin (builds up)
    - Reduced hepatic gluconeogenesis

Other Oral Medications

- **Thiazolidinediones (pioglitazone)** -
  - do not increase insulin secretion directly or cause hypoglycemia
  - improve liver histology (decreased liver fat and necro-inflammation, stable or improved fibrosis) and now considered the best option for treating NAFLD/NASH.
  - concern regarding fluid retention in patients with cirrhosis

- **Alpha-glucosidase inhibitors (acarbose)** could be useful in patients with cirrhosis:
  - reduce carbohydrate absorption in the bowel, which would decrease the risk of postprandial hyperglycemia
  - possibly reduce risk of hepatic encephalopathy

Pharmacokinetics, safety and tolerability of empagliflozin, a sodium glucose cotransporter 2 inhibitor, in patients with hepatic impairment

Conclusion:

- Empagliflozin was well tolerated in subjects with hepatic impairment.
  - Increases in empagliflozin exposure were less than twofold in patients with hepatic impairment;
- Therefore ***no dose adjustment of empagliflozin is required in patients with hepatic impairment.***

- SGLT2i might be helpful in treating **ascites due to cirrhosis** – preliminary studies – more needed
  https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/cld.714

Clin Pharmacokinet. 2014 Sep;53(9):773-85. doi: 10.1007/s40262-014-0157-y.

Pharmacokinetics in Patients With Chronic Liver Disease and Hepatic Safety of Incretin-Based Therapies for the Management of Type 2 Diabetes Mellitus

André J Scheen

- Only mild changes in pharmacokinetic characteristics of **DPP-4 inhibitors** were observed in patients with different degrees of hepatic impairment (HI), presumably without major clinical relevance.
- **GLP-1 receptor agonists** have a *renal excretion* rather than liver metabolism – no dose adjustment needed
- No significant changes in liver enzymes were reported with DPP-4 inhibitors or GLP-1 receptor agonists, alone or in combination with various other glucose-lowering agents, in clinical trials up to 2 years in length.
  - preliminary data suggested that incretin-based therapies may be beneficial in patients with CLD, more particularly in the presence of non-alcoholic fatty liver disease.

Still in process of learning about effectiveness & impact

Insulin therapy

- Caution regarding the dosage of insulin therapy
  - insulin requirements in patients with cirrhosis may vary depending on the severity of cirrhosis.
    - In patients with ***compensated cirrhosis***, ***insulin requirement*** may be ***increased slightly*** because insulin resistance predominates.
    - In patients with ***decompensated cirrhosis***, the hepatic metabolism of insulin is reduced, which ***decreases the needs for insulin*** (reduced clearance, also reduced ability of the liver to respond to low BG)

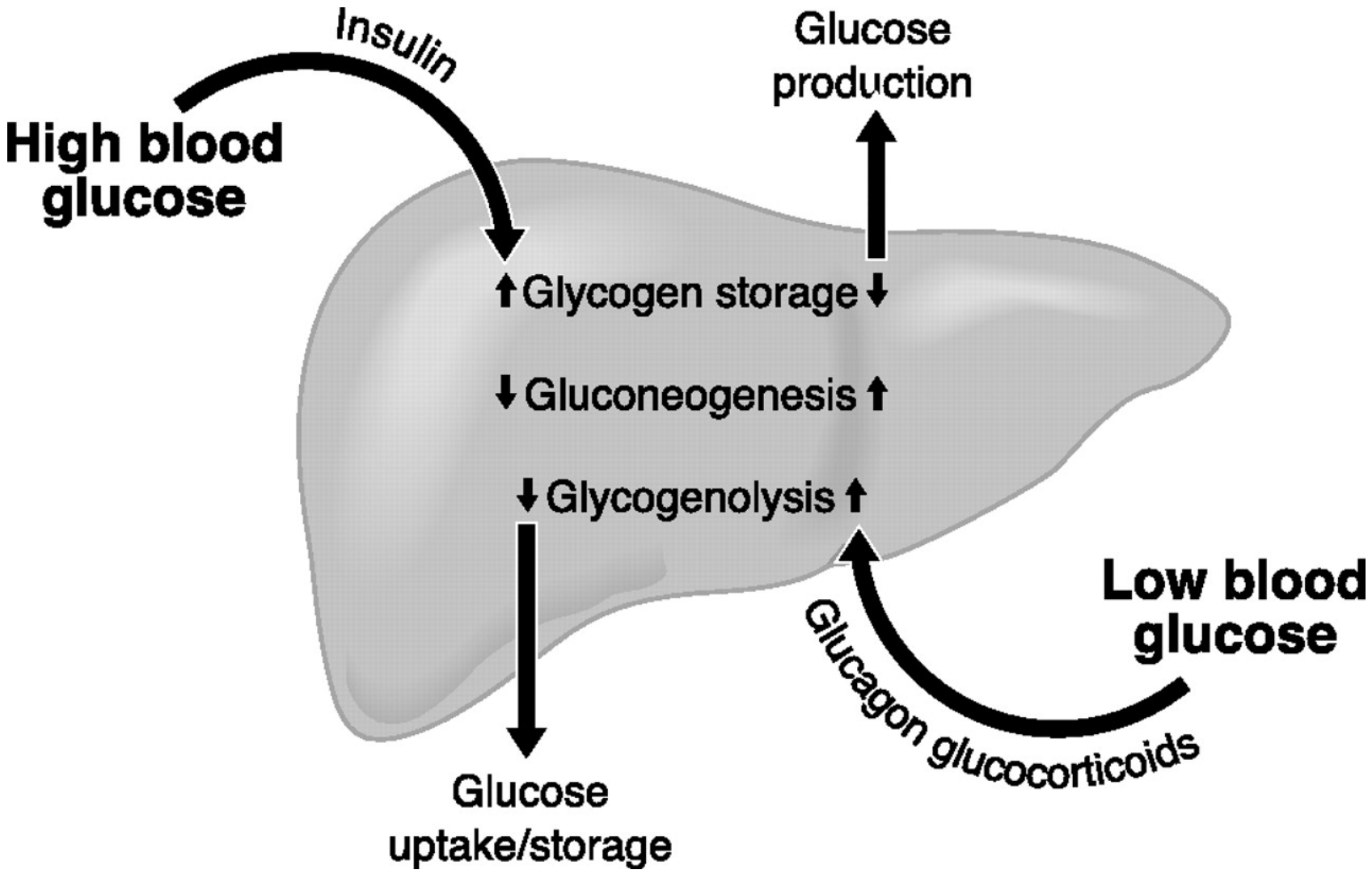
Summary

- Diabetes increases fibrosis in liver disease→ cirrhosis
- Diabetes complicates cirrhosis→ increased morbidity (risk of cirrhosis complications) & mortality
- Cirrhosis can cause abnormal glucose metabolism
  - Hepatogenous diabetes
- A1c is unreliable in cirrhosis (tends to be falsely low)
  - ? Role of CGM
- 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

END

- Extra Slides

Liver plays key role in glucose homeostasis



Diabetes & Hepatic Fibrosis

- **Hepatic stellate cells**, in a chronically injured liver, *promote liver fibrosis* through excessive extra-cellular matrix production and reduced extra-cellular matrix degradation.
- Glucose and insulin have profibrogenic properties on hepatic stellate cells.
- Hyperglycemia and oxidative stress contribute to the accumulation of advanced-glycation-end (AGE) products.
  - Receptors for AGE products are overexpressed & up-regulated in activated hepatic stellate cells
    - This suggests that insulin and hyperglycemia may also activate hepatic stellate cells through attachment of AGE products on their receptors.

Advanced-glycation-end-products (AGEs)

- Hyperglycemia fosters the AGEs
- AGEs could also induce insulin resistance and beta-cell injury prior to diabetes onset
- the kidney & the liver are involved in the removal of AGEs
  - in patients with cirrhosis without diabetes, plasma AGE levels are markedly elevated and correlate with the severity of the liver disease
  - after liver transplantation, a clear decline in AGEs levels occurs
  - speculated that in patients with cirrhosis, the accumulation of AGEs, related to a reduced removal of AGEs, may promote diabetes (damage Beta cells?)

SGLT2i & NAFLD

- In a number of studies, treatment with SGLT2 inhibitors resulted in a reduction in hepatic steatosis and in transaminase levels.
  - However, existing studies are small, their follow-up period was short, and none evaluated the effects of SGLT2 inhibitors on liver histology.
  - Accordingly, larger studies are needed to verify these preliminary results and define the role of SGLT2 inhibitors in the treatment of NAFLD in patients with T2DM.