MASH e diabete
Fisiopatologia: uovo o gallina?

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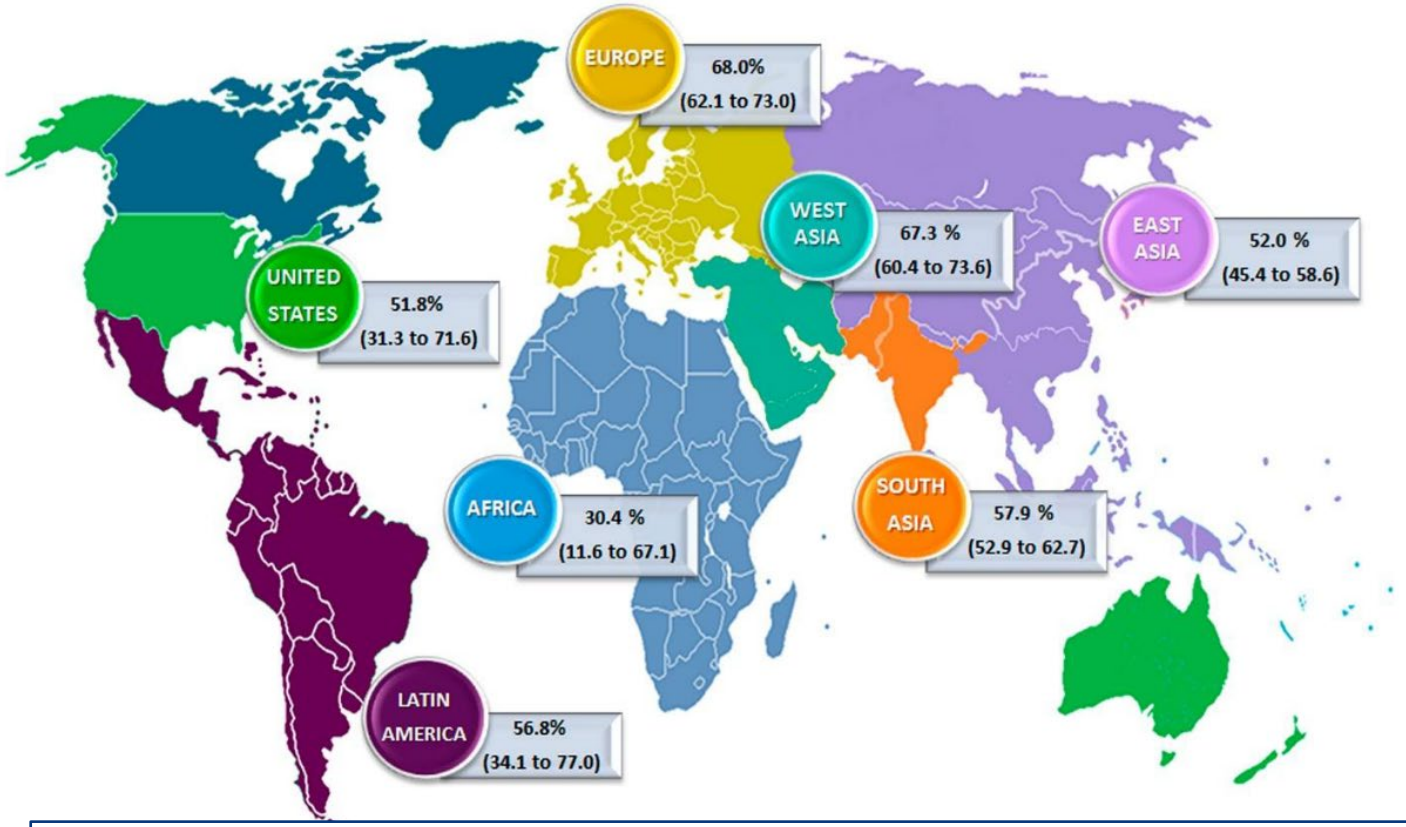
Conflict of interest

PRESENTER DISCLOSURE
Dr. Amalia Gastaldelli

Advisory Boards/consultant: Boehringer Ingelheim and Novo Nordisk, Eli-Lilly, Fractyl, Pfizer, Merck-MSD, Metadeq
Speaker's honorarium/other fees: Eli-Lilly, Novo Nordisk, Madrigal, Echosense and Pfizer

High prevalence of MASLD and strong Strong correlation with T2D



- **The global prevalence of MASLD in T2D is 67% (was 55%)**
- **The global prevalence of MASH in T2D is 41% (was 37.3%)**
- **Advanced fibrosis/cirrhosis 38% (was 17%) in those who had a liver biopsy**

MASLD diagnosed by Ultrasound or MRI-MRS

Diabetes predictions WORLD

2045 700 million
2030 578 million
2019 463 million

↑ 51% increase

IDF Atlas 9th edition

Europe

2045 68 million
2030 66 million
2019 59 million

↑ 15% increase

MASLD is associated with a 2.2-fold increased risk of developing diabetes. (Mantovani Gut 2021)

Prediction of global prevalence of in 2045

- **MASLD+T2D 469 million**
- **MASH+T2D 286 million**

Change in nomenclature/diagnosis

NAFLD ⊖

Non-alcoholic Fatty Liver Disease

Ludwig et al 1980

LIVER STEATOSIS

Exclusion
alcohol consumption
(M<30 and F<20 g/day)

Exclusion
any other secondary cause of hepatic steatosis

- Isolated steatosis **NAFL**
- Steatohepatitis **NASH** by liver biopsy

MAFLD ⊕

Metabolic (dysfunction) Associated Fatty Liver Disease

Eslam et al 2020

LIVER STEATOSIS AND

Lean/normal weight
BMI<25 kg/m2 +
≥ 2 metabolic risk factors
↑ Waist circumference
↑ Blood Pressure
↑ Triglycerides
↓ HDL
↑ C-reactive protein
Prediabetes
HOMA≥2.5

Overweight/ Obesity
BMI≥25 kg/m2

Type 2 Diabetes

No mention of alcohol intake

MASLD ⊕

Metabolic (dysfunction) Associated Steatotic Liver Disease

Rinella et al 2023

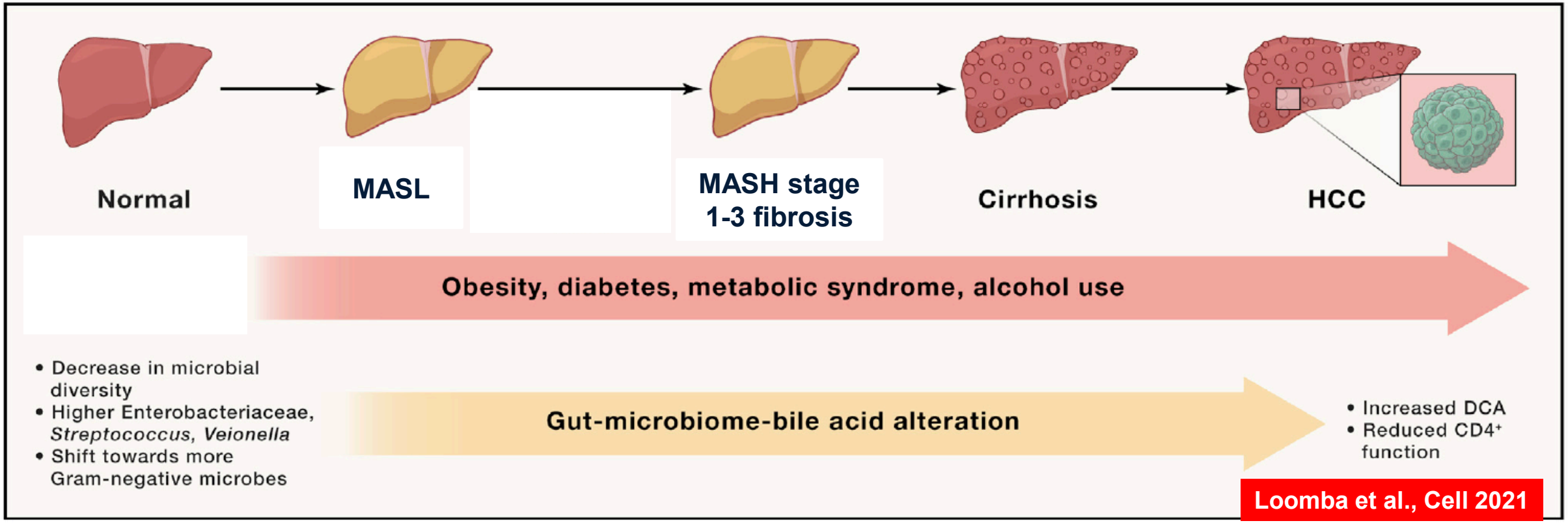
LIVER STEATOSIS AND

at least 1 metabolic risk factor in the absence of excessive alcohol consumption
(M<30 and F<20 g/day)

- Isolated steatosis **(MASL)**
- Steatohepatitis (**MASH)** by liver biopsy

MetALD:
MASLD AND
increased alcohol intake
(F: 20–50; M: 30–60 g/day)

What the term MASLD includes



Who are at risk? (Estimated prevalence is 38% of all adults)

Diagnosis of MASLD remains incidental

EASL EASD EASO guidelines 2024

Diagnosis of MASLD is incidental!!!

Guidelines suggest screening for fibrosis in high-risk population because critical for the management of liver disease

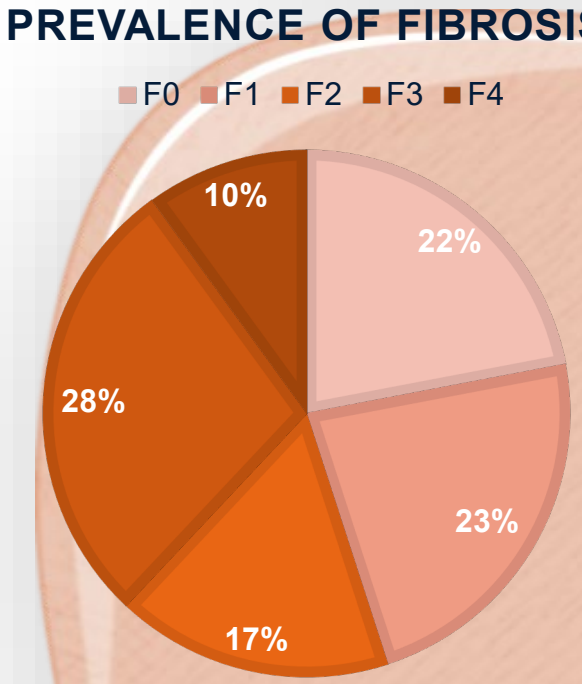
- Presence and severity of liver fibrosis correlates with prognosis
- Presence of cirrhosis identifies patients at risk of:
  - Clinical decompensation
  - Liver-related mortality
  - Hepatocellular carcinoma

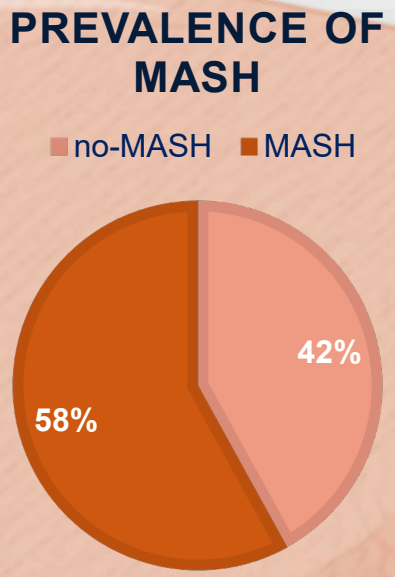
Association of fibrosis and cirrhosis with prognosis and clinical progression is irrespective of aetiology

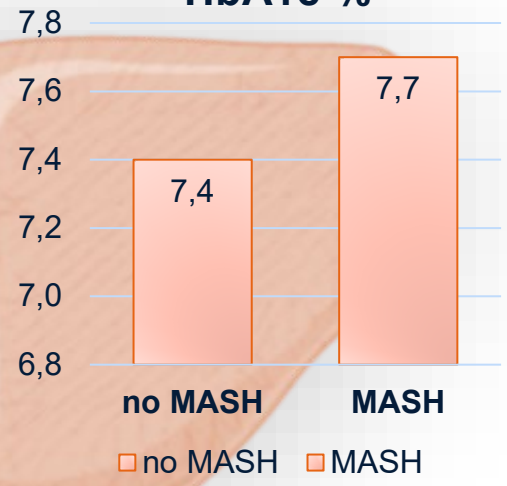
Quale è la prevalenza di MASH nei T2D con ALT > 20-30U/L?

A. 30%
B. 40%
C. 50
D. >50%

Higher Fibrosis and HbA1C in subjects with T2D and MASH

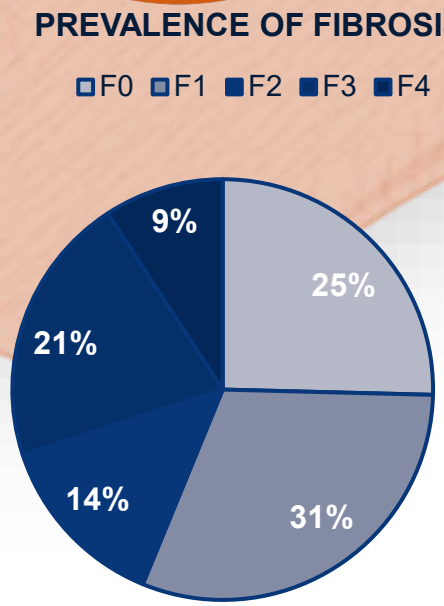


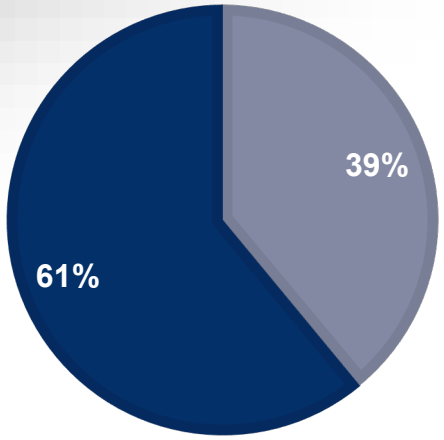


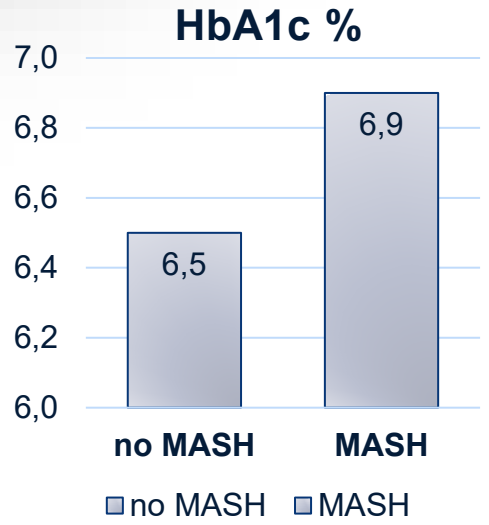


POPULATION
Patients with liver biopsy
ALT F>20 U/L M> 30 U/L
(mean value ALT 49U/L)
65% with obesity

Castera et al Diabetes Care 2023

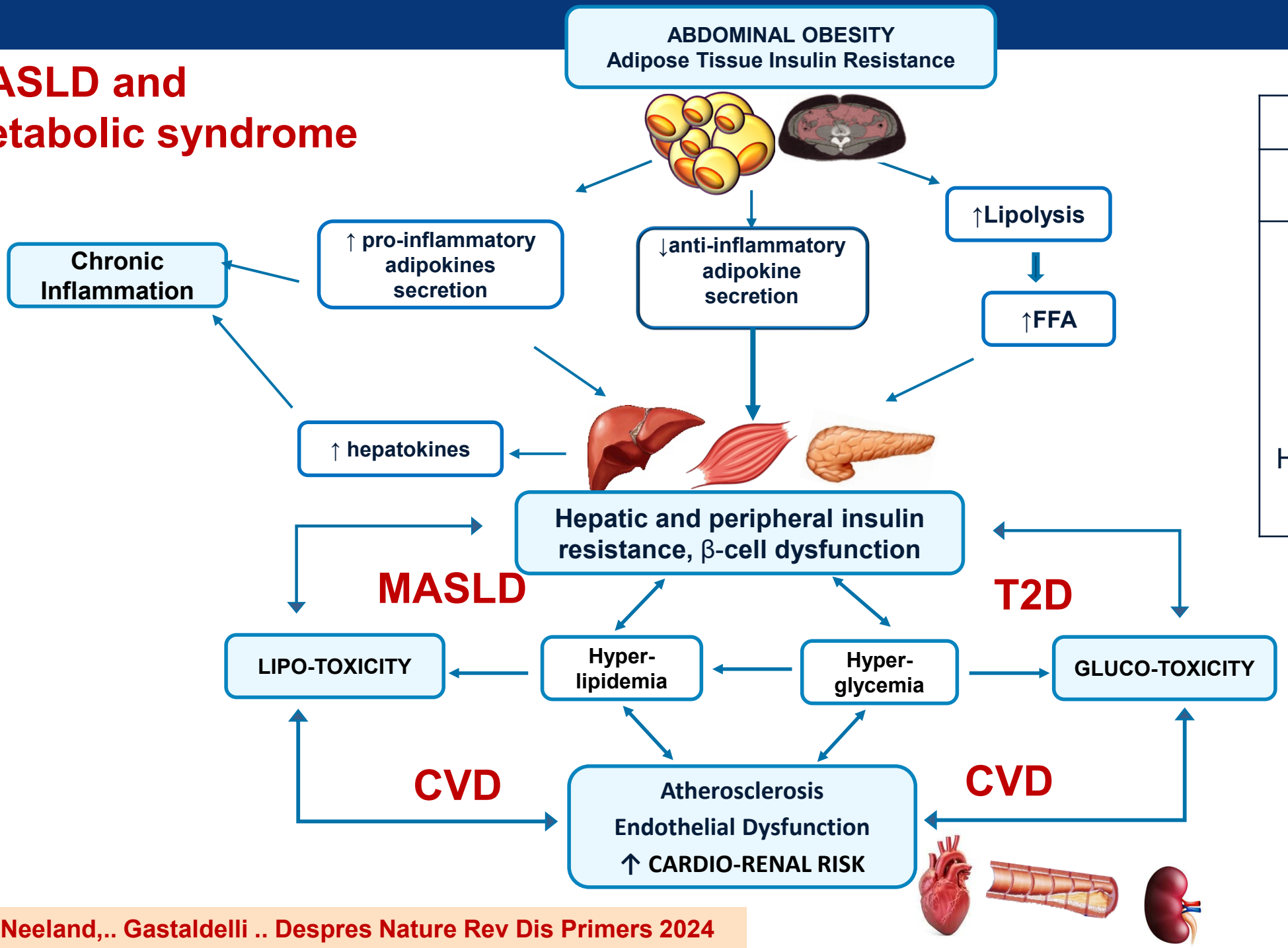






Ajmera et al J Hepatol 2023

MASLD and Metabolic syndrome



MASLD
Liver steatosis + ⩾1 criterium
Abdominal obesity
Dysglycemia
Hypertension
Low HDL
Hypertriglyceridemia
Insulin resistance

from Neeland,.. Gastaldelli .. Despres Nature Rev Dis Primers 2024

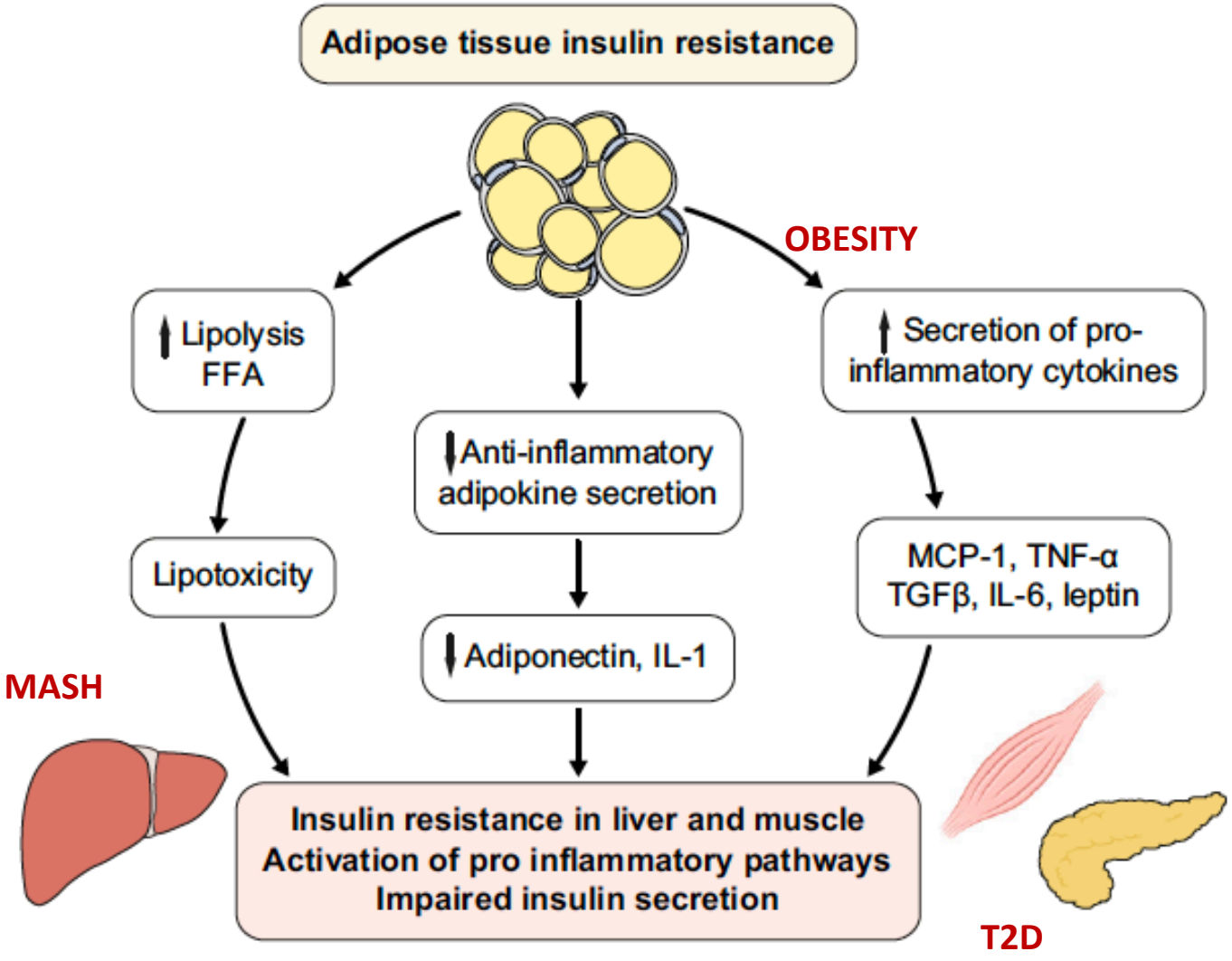
Mechanisms: Lipid metabolism

MASLD
Liver steatosis + ⩾1 criterium
Abdominal obesity
Dysglycemia
Hypertension
Low HDL
Hypertriglyceridemia
Insulin resistance

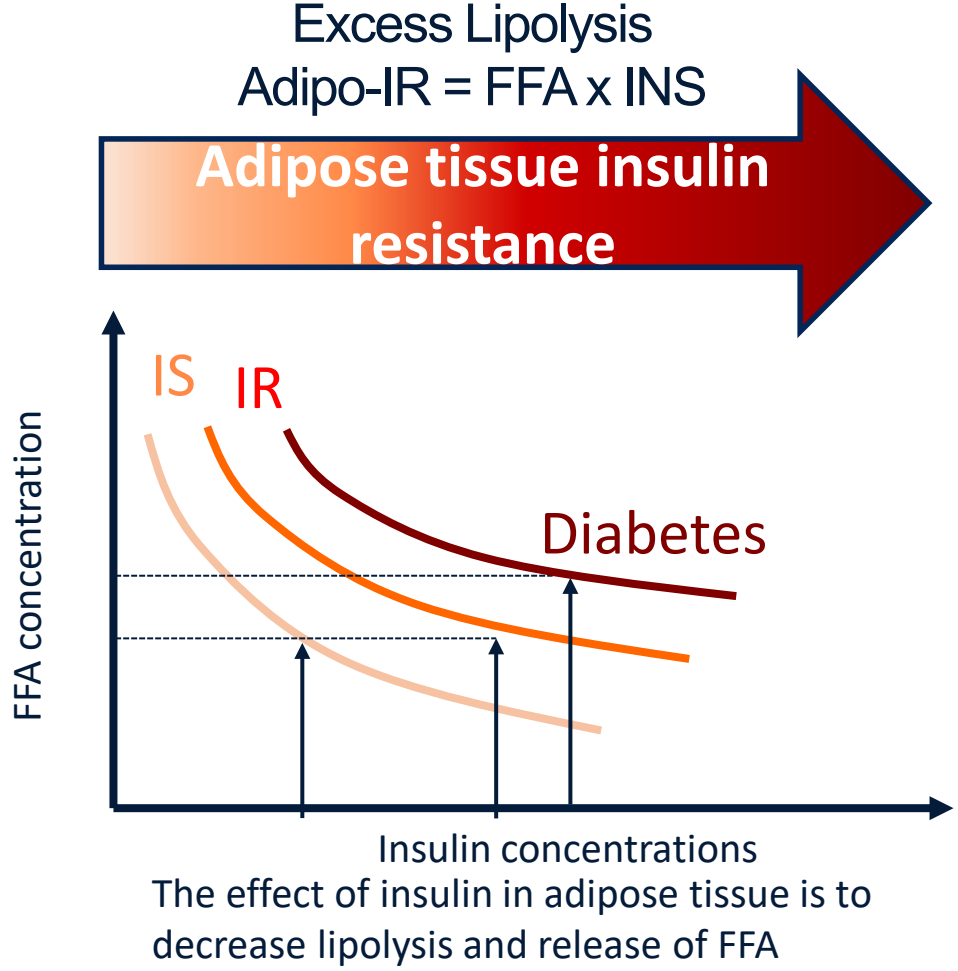
- **Dysfunctional adipose tissue and IR**
- **Excess lipolysis**
- **Excess abdominal obesity**
- **Hepatic lipoprotein synthesis**
- **Hepatic De Novo Lipogenesis (DNL)**

Rinella et al J Hepatol 2024

Adipose tissue insulin resistance and dysfunction is associated with MASLD and T2D



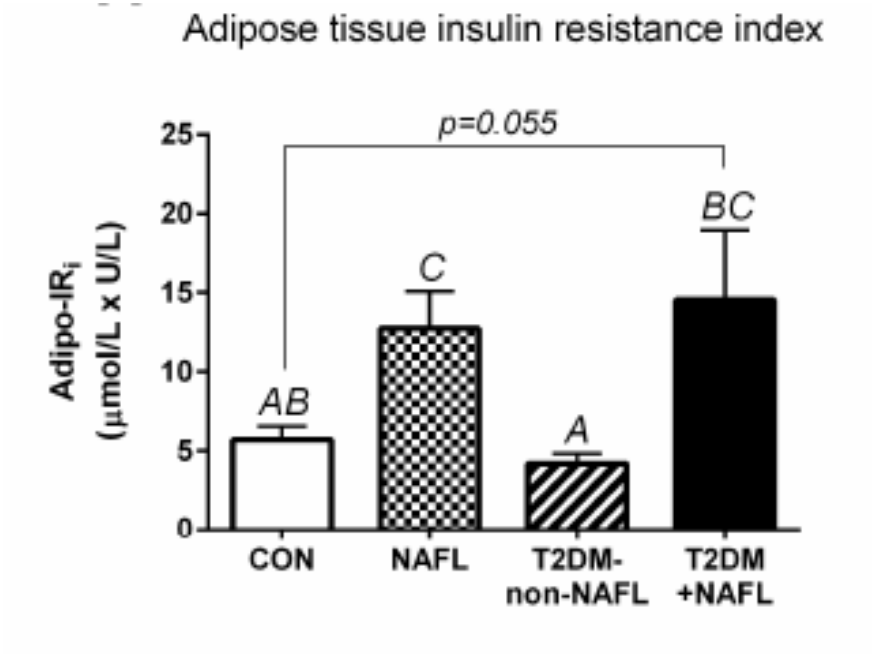
Gastaldelli & Cusi JHEP Rep 2019, Klein et al Cell Metab 2022



The effect of insulin in adipose tissue is to decrease lipolysis and release of FFA

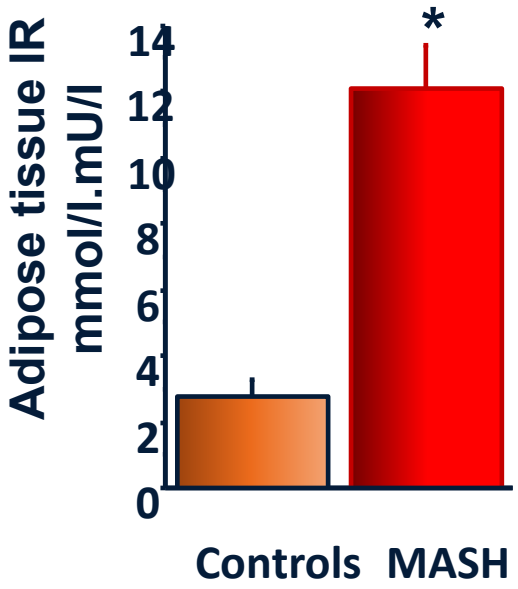
Groop et al JCI 1989, Gastaldelli et al Gastroenterology 2007

↑ Adipose tissue insulin resistance in MASH and T2D

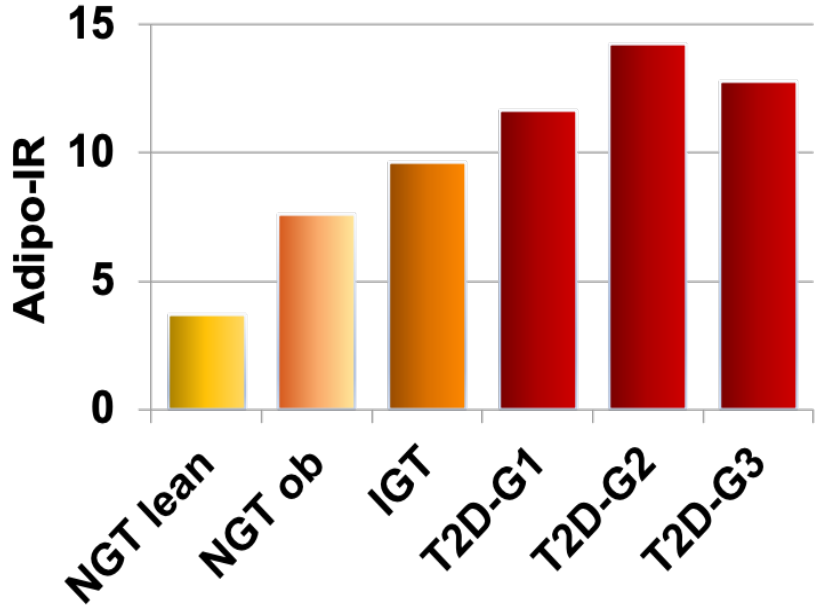


Brouwers B et al Clinical Sci 2017

Adipo-IR = FFA x INS



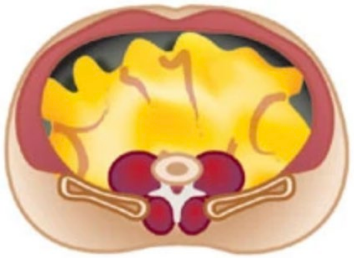
Gastaldelli et al Hepatology 2009



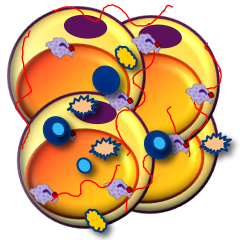
Gastaldelli et al Diabetes 2017

T2D-Groups divided according to 2h-PG:
G1 <300 mg/dL, G2 300-360 mg/dL,
G3 >360 mg/dL

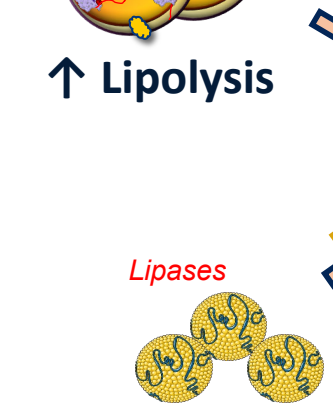
What is the impact of abdominal obesity?

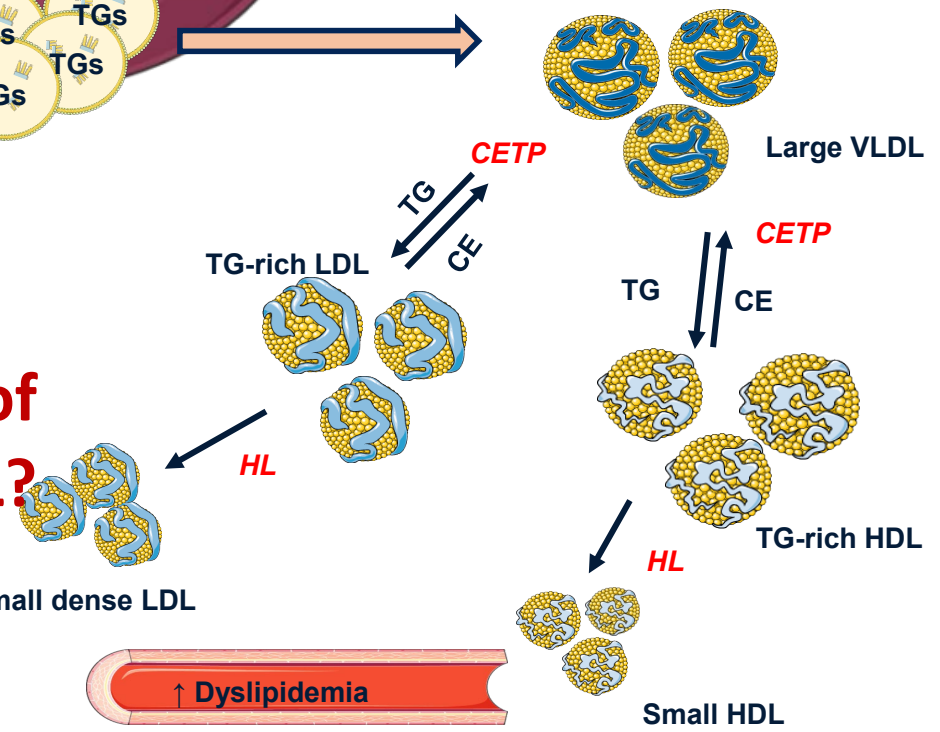


Adipose tissue IR



↑ Lipolysis

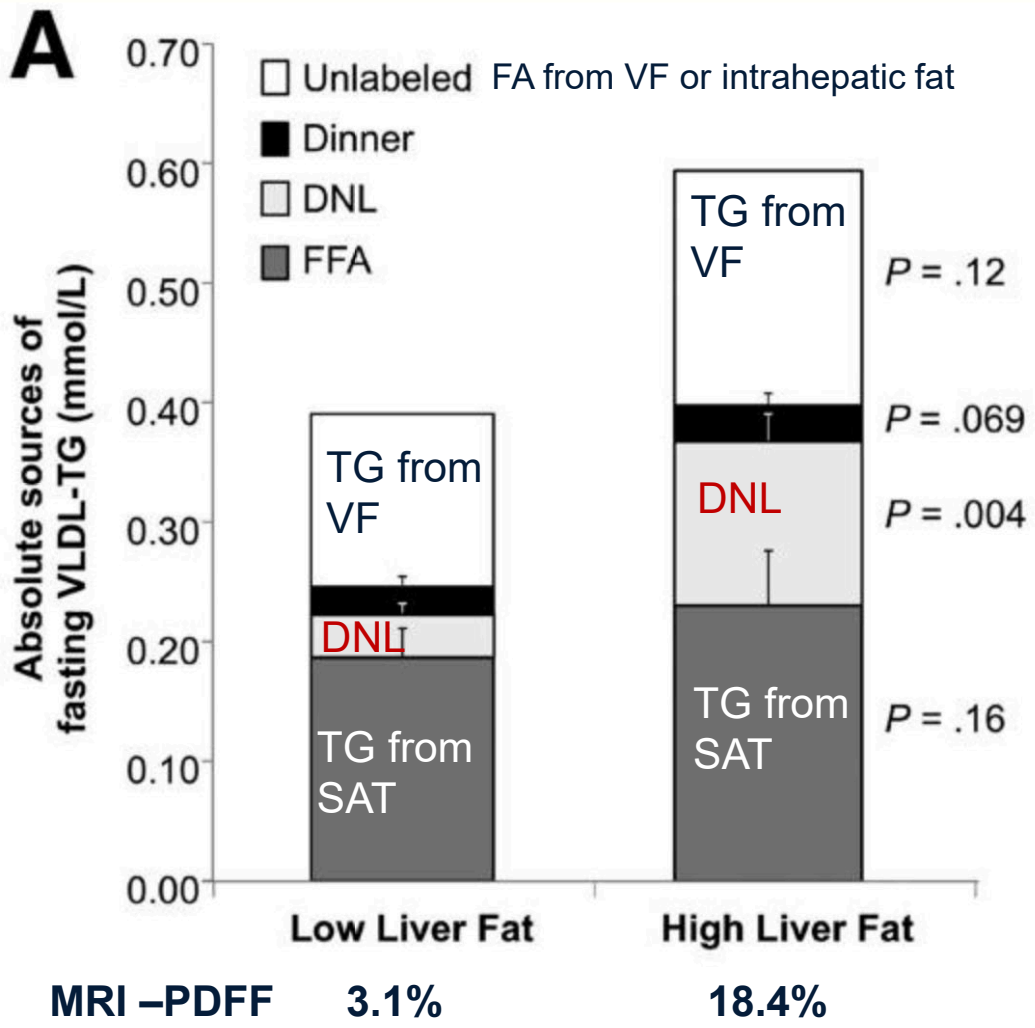


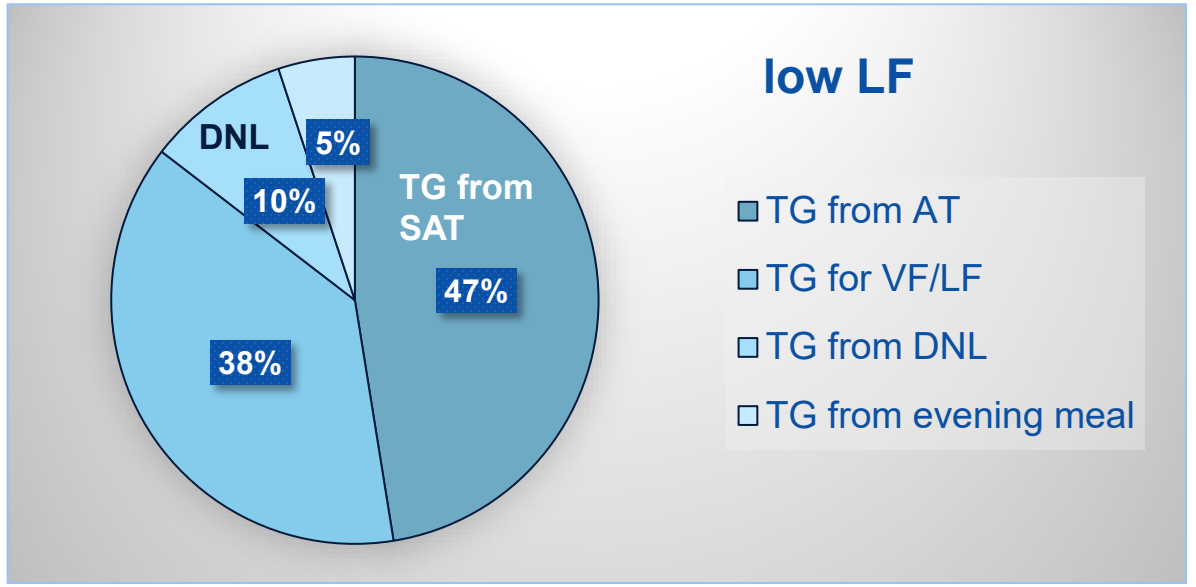


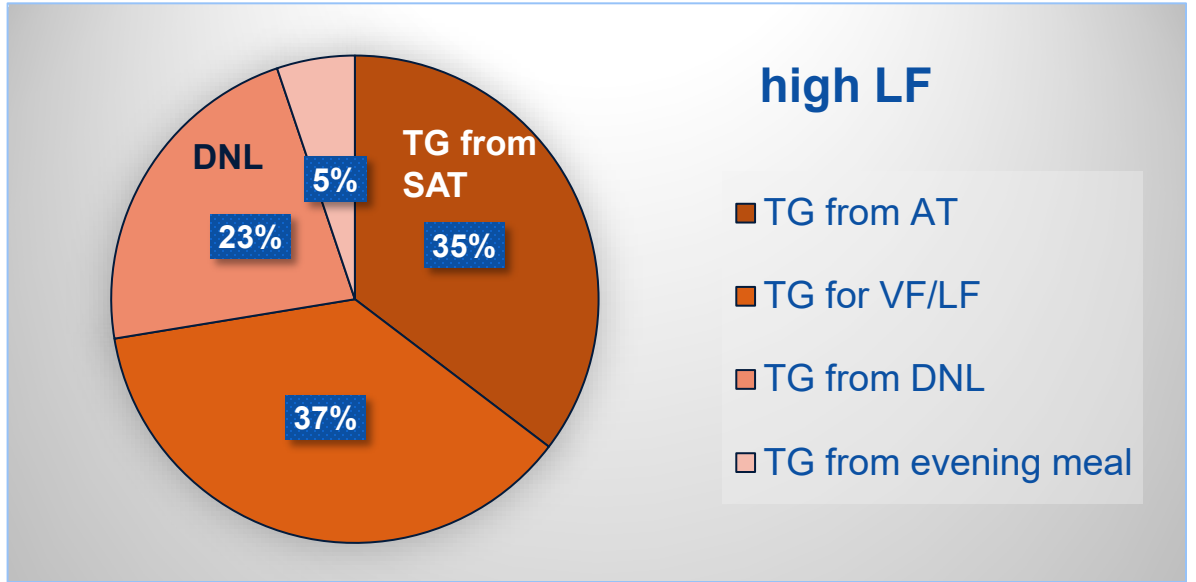
What is the impact of VLDL secretion and DNL?

F Carli, G Della Pepa, S Scoditti , AJ Vidal-Puig, A Gastaldelli JHep Reports 2024

Composition of VLDL triglycerides after a standardized evening meal

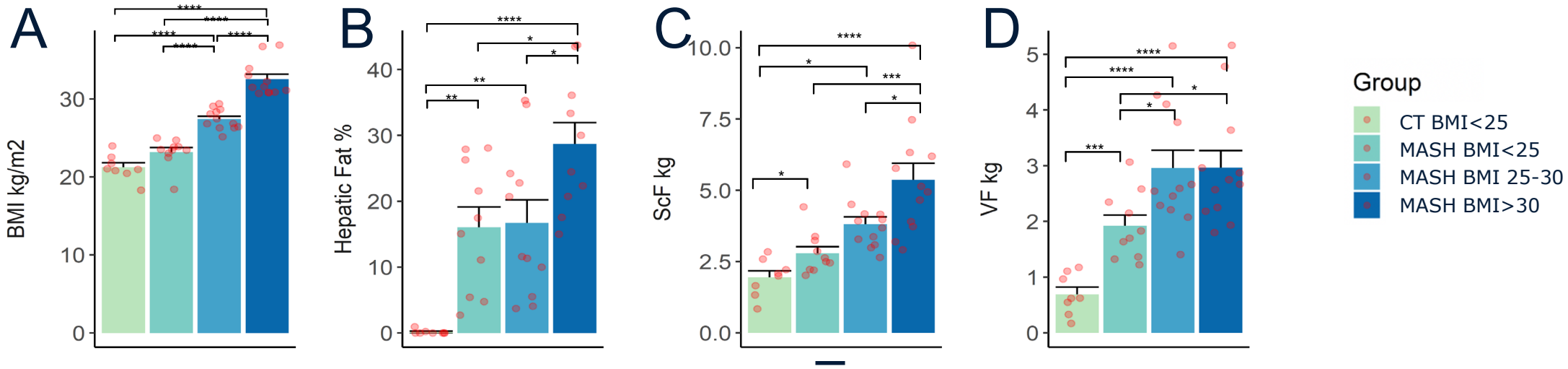


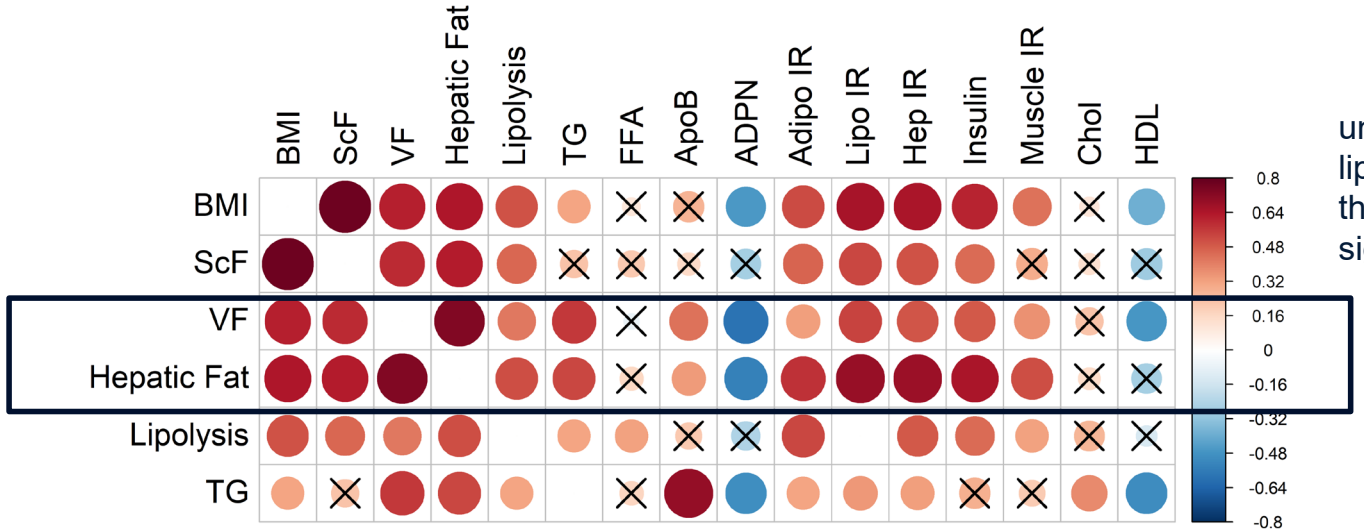




Lambert et al Gastroenterology 2014

Visceral fat is increased already in subjects with MASH and BMI<25 kg/m^2 and correlates with IR and lipolysis





univariate correlation matrix between BMI, fat distribution, lipolysis and circulating TG and metabolic parameters in the entire cohort. Correlations that are not statistically significant (Pearson's p-value≥0.05) were crossed out.

Saponaro et al Liver Int 2022

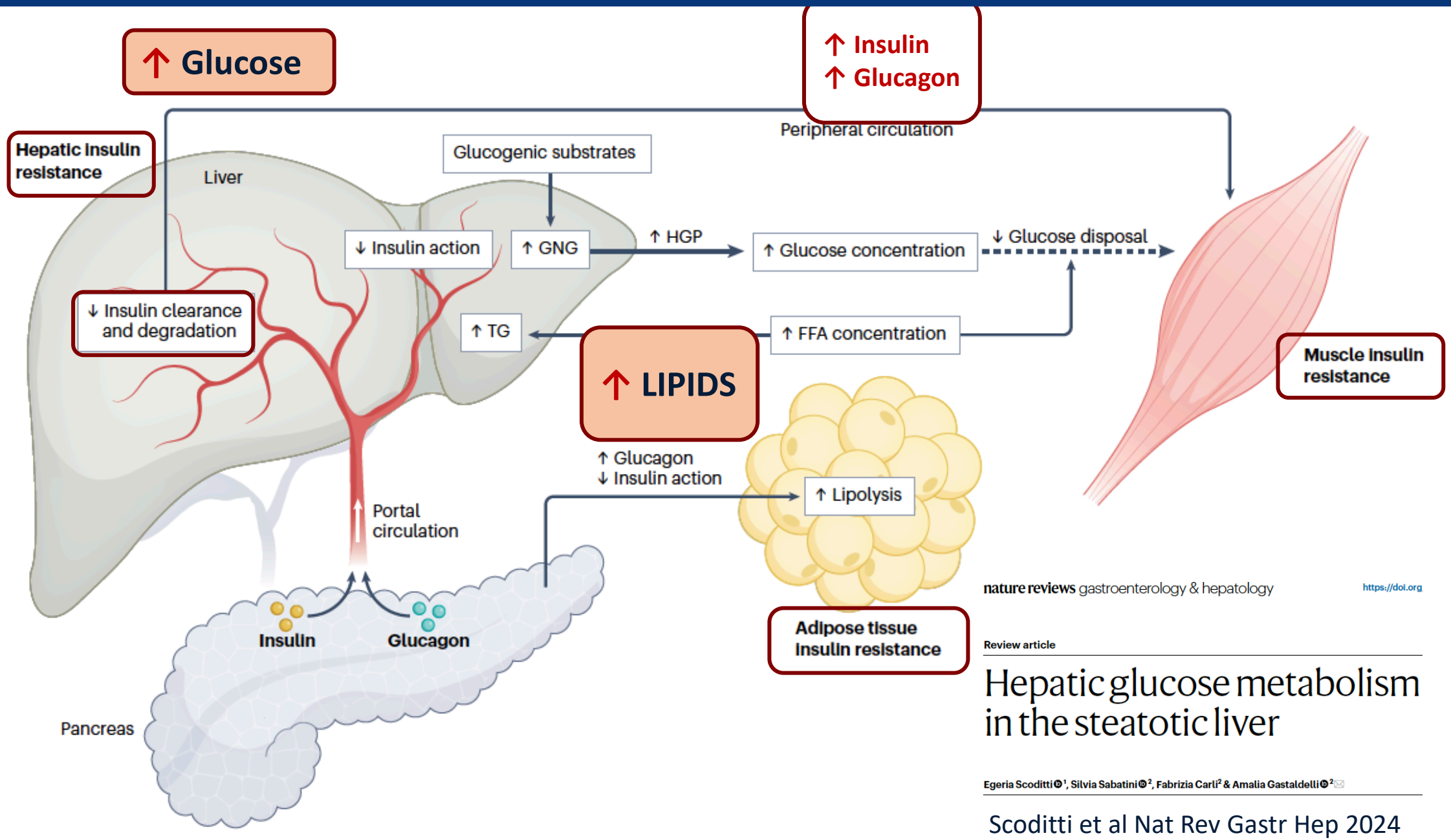
Mechanisms: Glucose metabolism

MASLD
Liver steatosis + ⩾1 criterium
Abdominal obesity
Dysglycemia
Hypertension
Low HDL
Hypertriglyceridemia
Insulin resistance

- **Fasting glucose metabolism**
- **Postprandial glucose metabolism**
- **Altered insulin secretion**

Rinella et al J Hepatol 2024

IR and increased metabolic fluxes in MASLD



nature reviews gastroenterology & hepatology https://doi.org

Review article

Hepatic glucose metabolism in the steatotic liver

Egeria Scoditti[1], Silvia Sabatini[2], Fabrizia Carli[2] & Amalia Gastaldelli[2]

Scoditti et al Nat Rev Gastr Hep 2024

MASLD have high fasting glucose

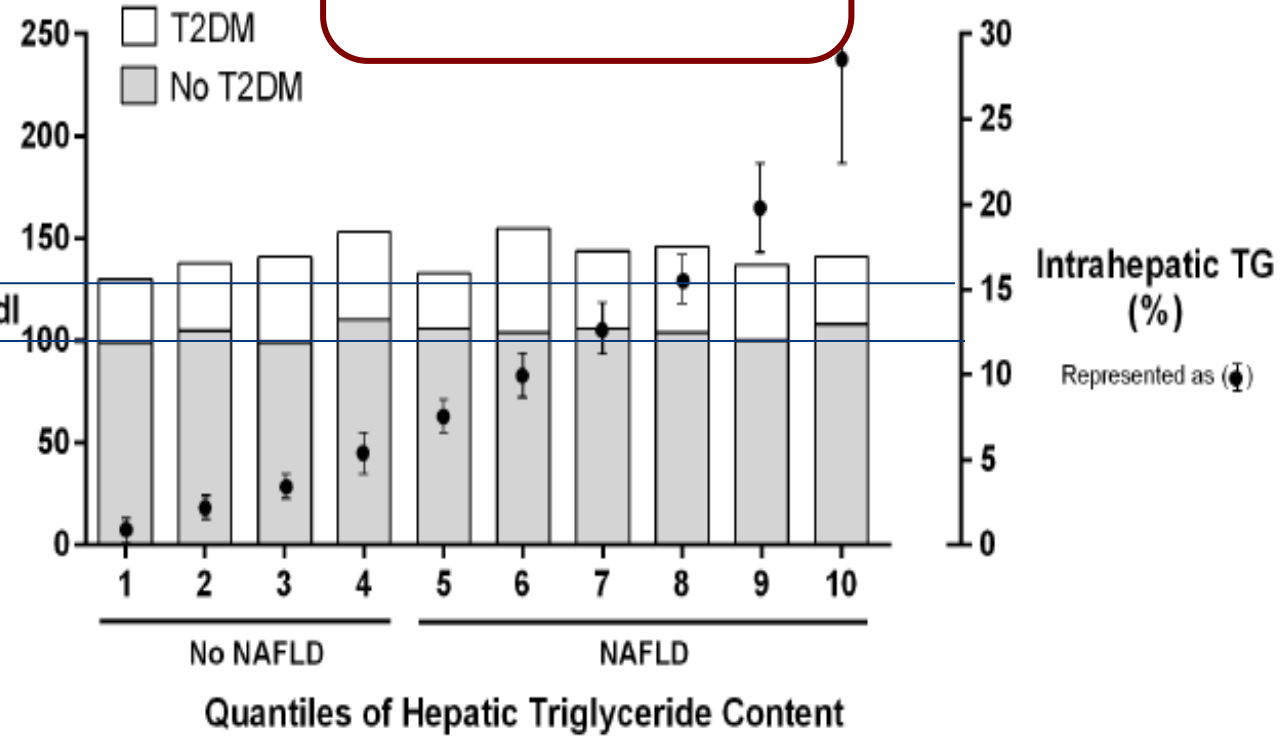
(Most MASLD have FPG>100 but no association with higher IHTG)

↑ Fasting Glucose Concentration

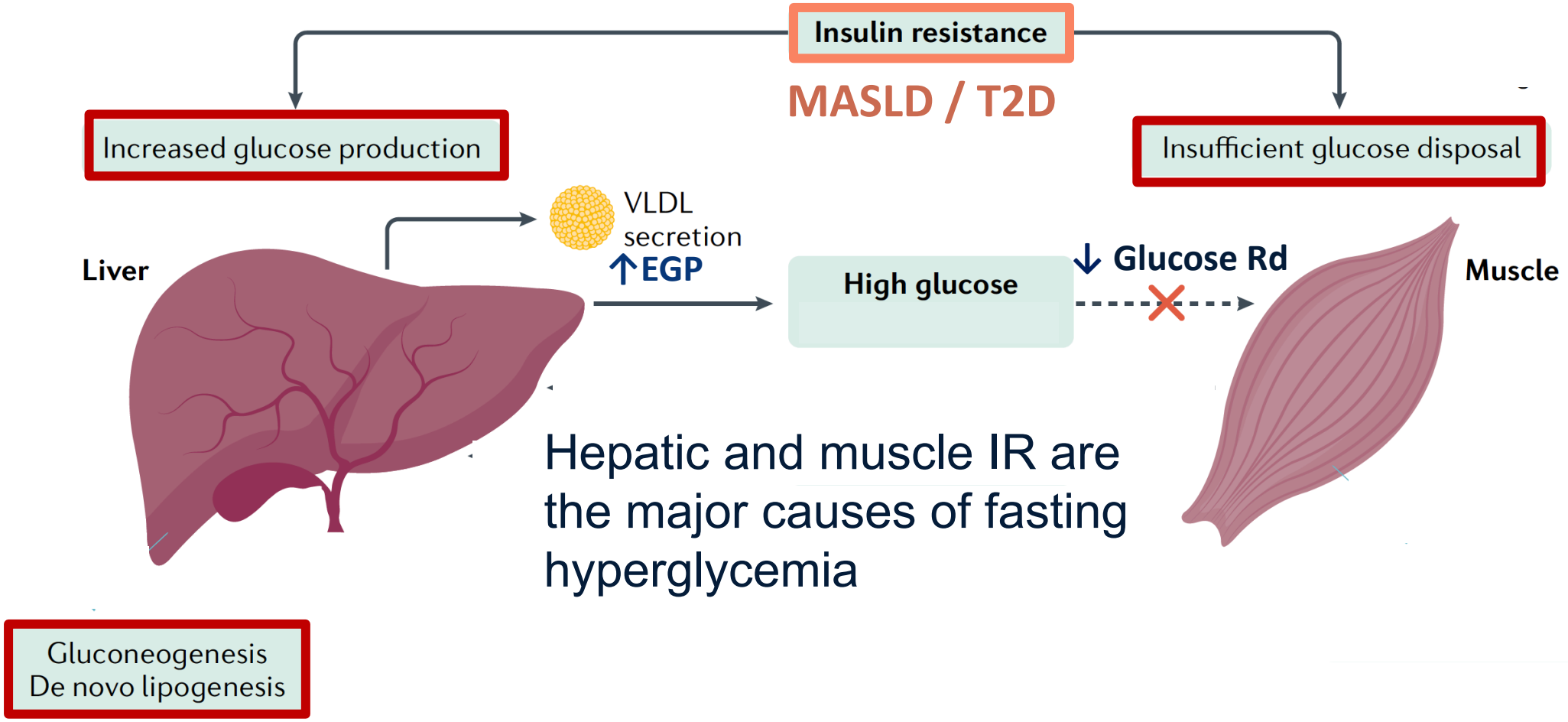
Diabetes

Pre-diabetes

Normal



Why MASLD have high fasting glucose?

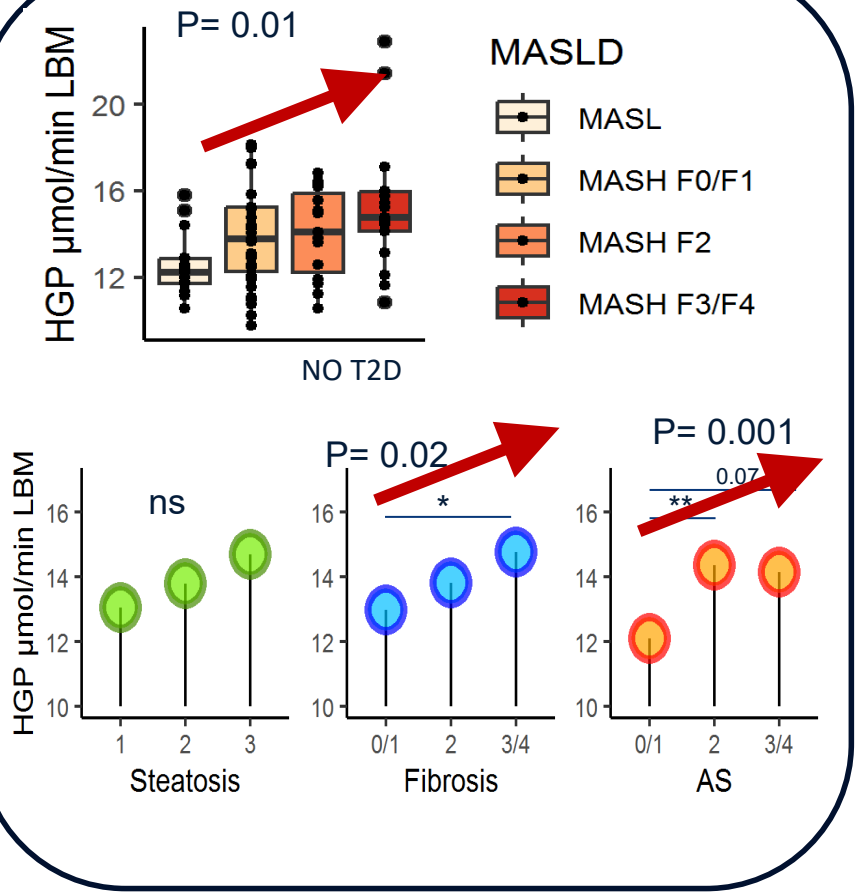


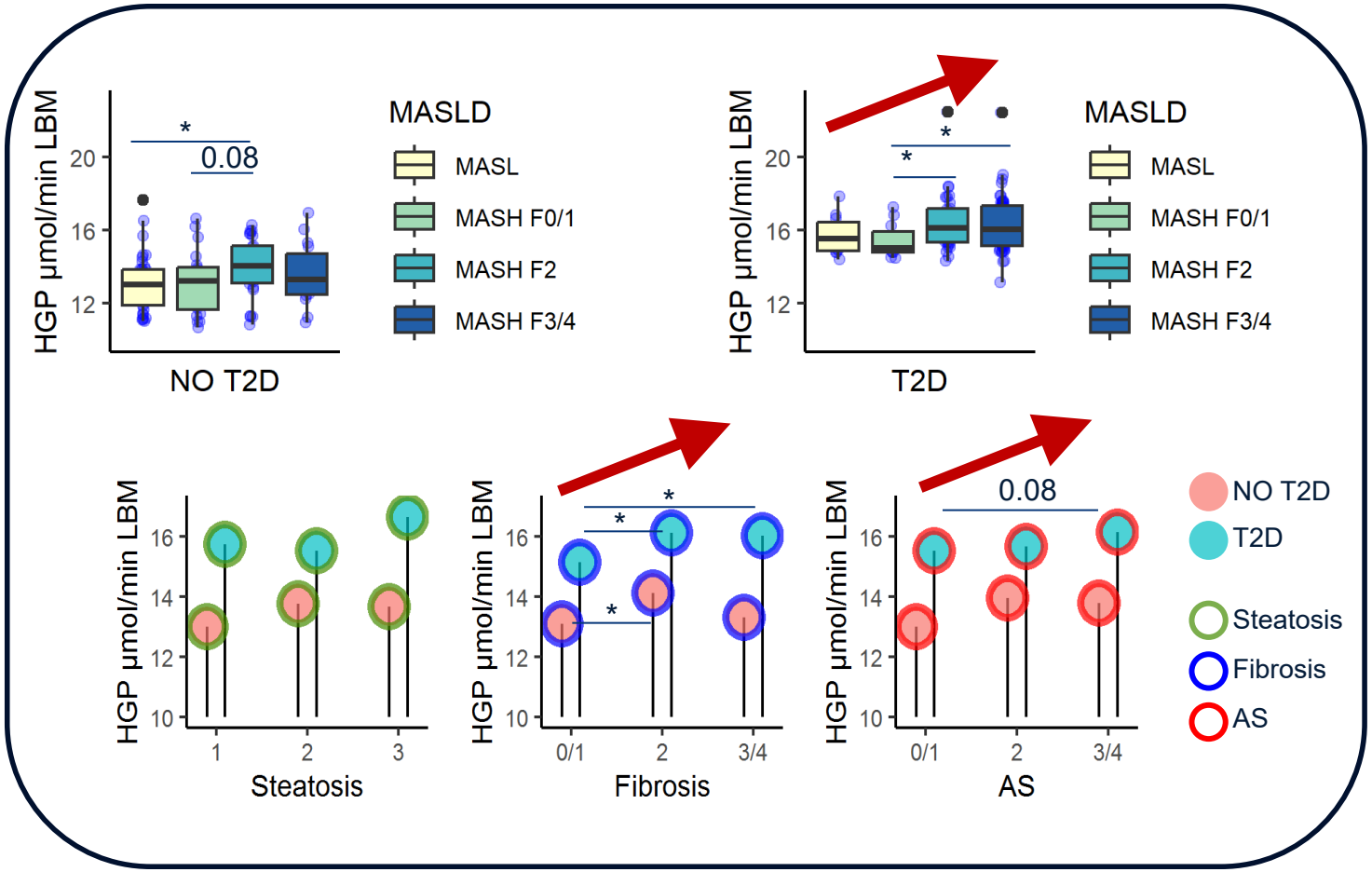
Masoodi Gastaldelli et al Nat Rev Gastr Hepatol 2021

HGP is increased with severity of MASH, hepatic inflammation and fibrosis not steatosis

Tracer Fluxomics cohort

Transcriptomics cohort



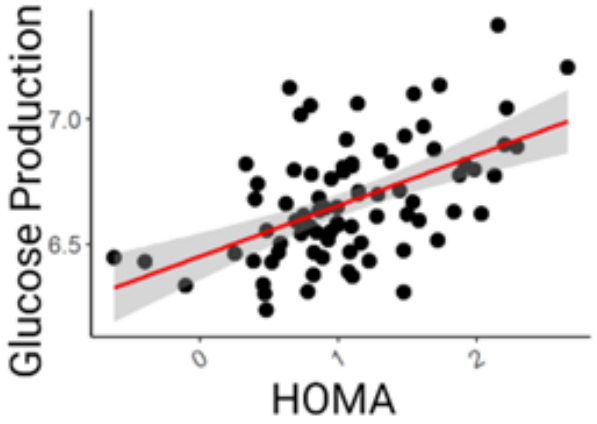


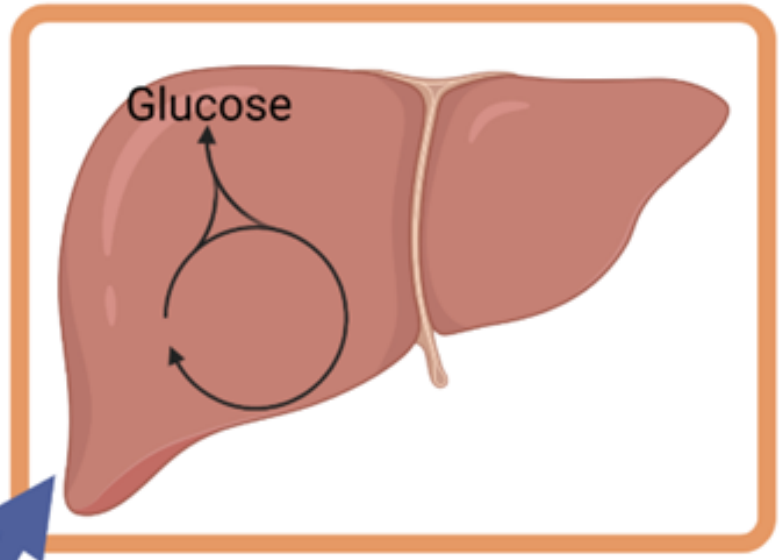
Sabatini et Cell Reports in Medicine 2024

Increased HGP is associated with lipolysis and HOMA-IR

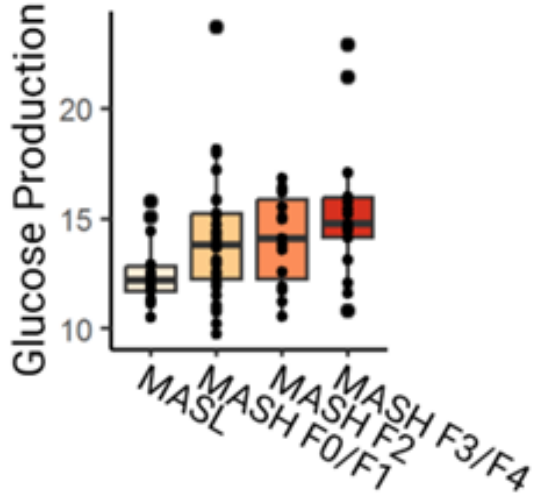
Tracer Fluxomics

Insulin Resistance

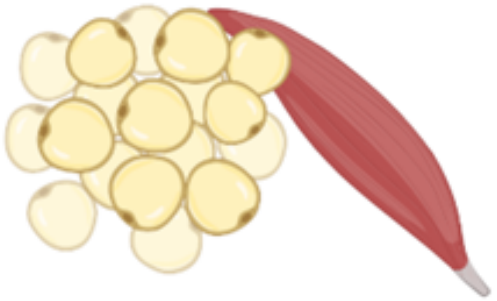


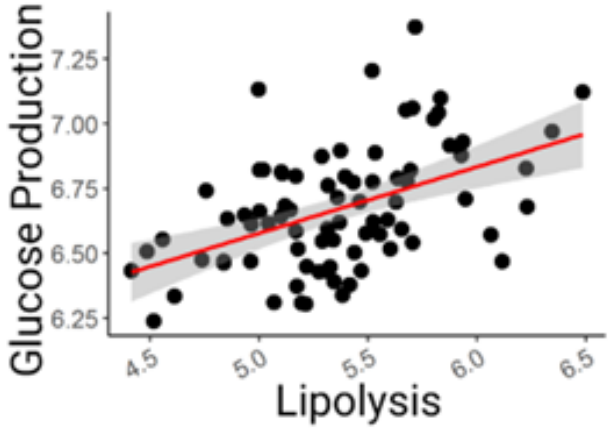


Glucose Production



Substrate availability





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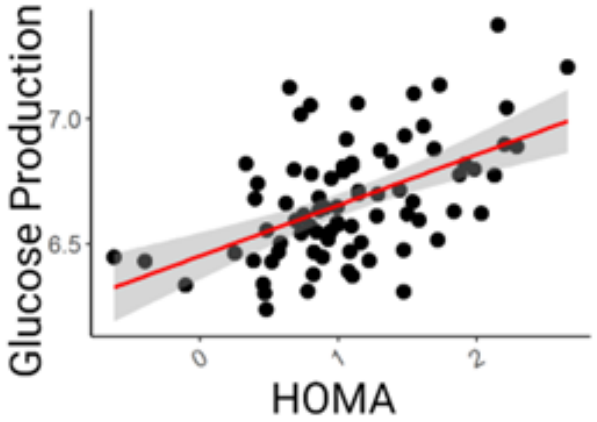
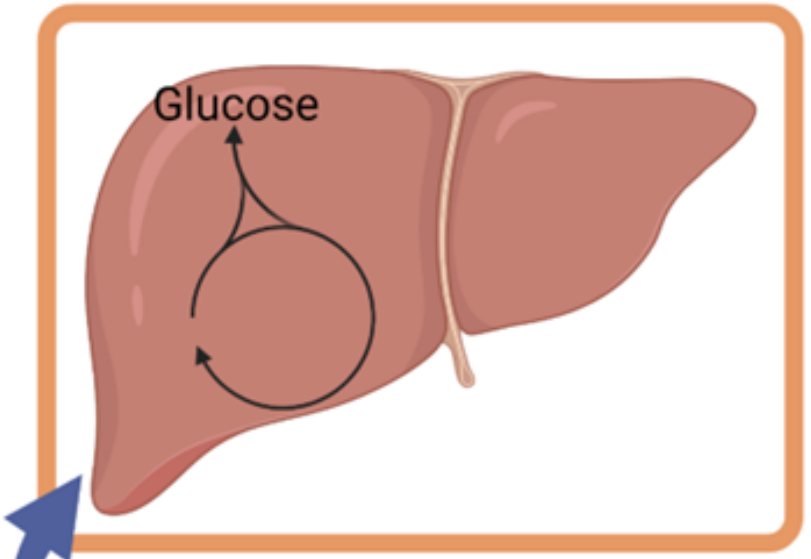
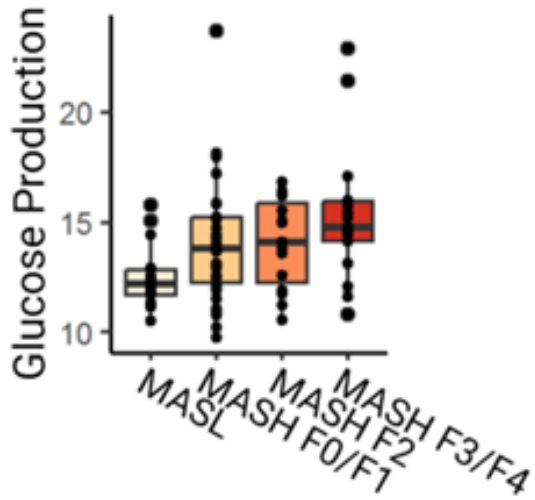
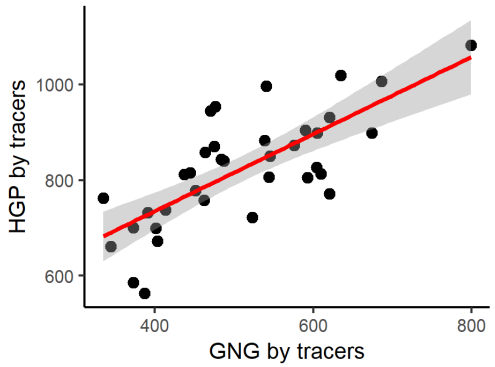


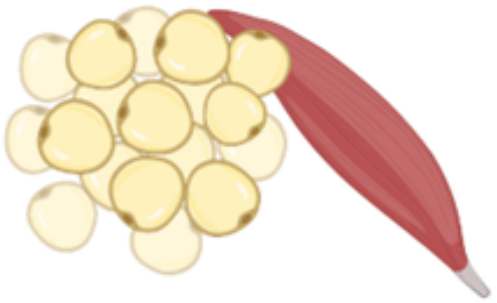


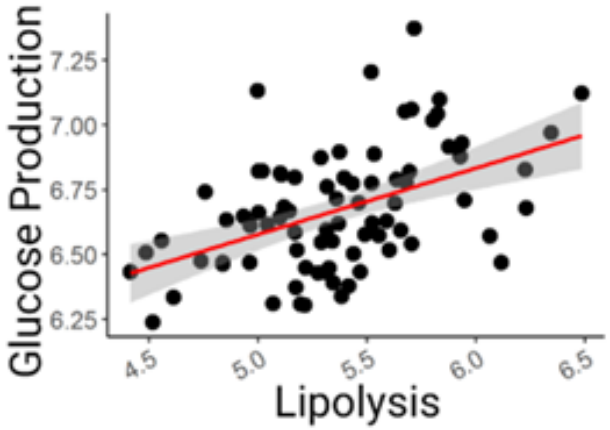
Glucose Production

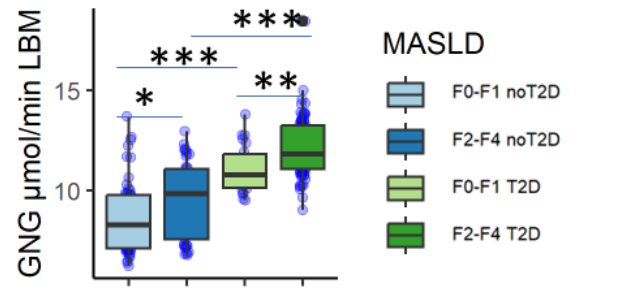




Substrate availability



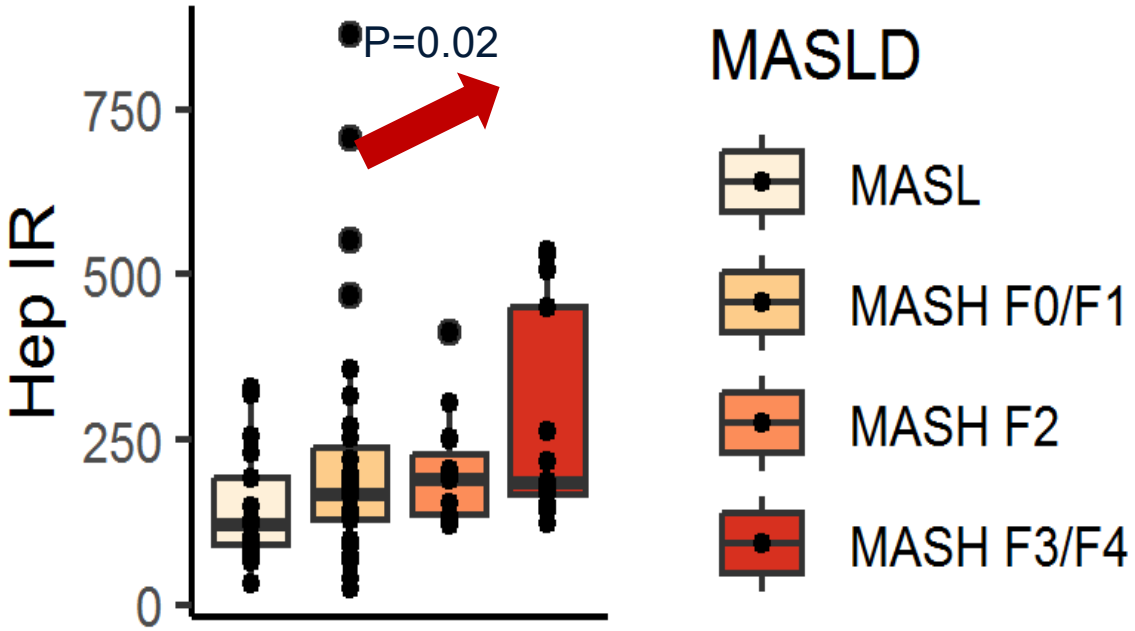




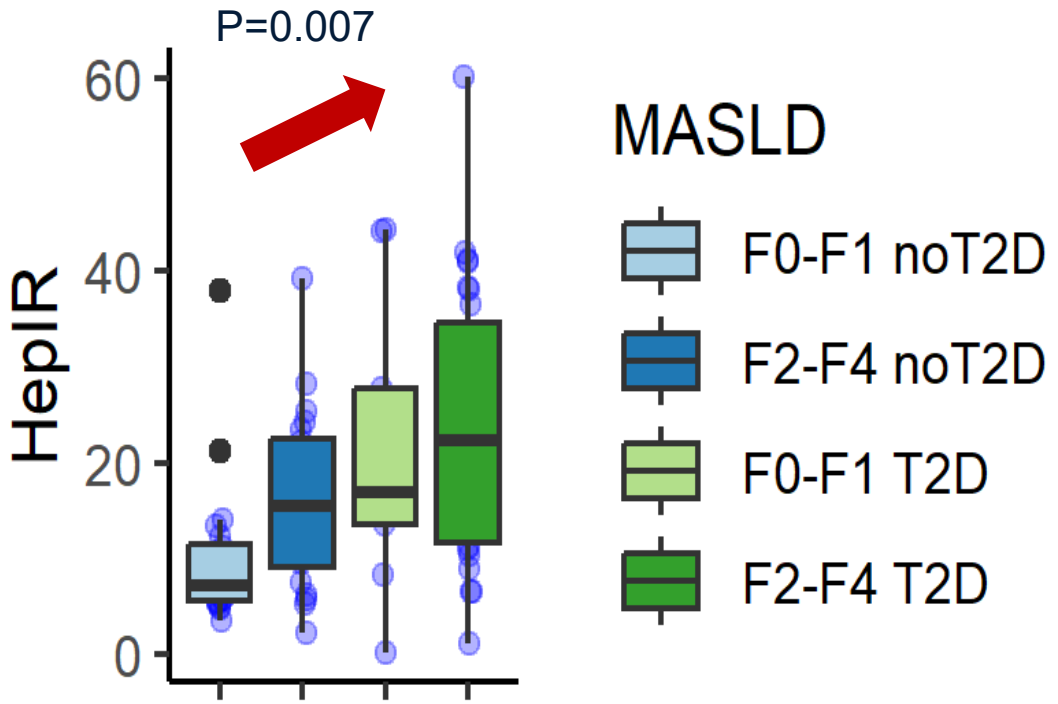
Sabatini et Cell Reports in Medicine 2024

Hepatic IR is increased in MASH with advanced fibrosis

Tracer Fluxomics

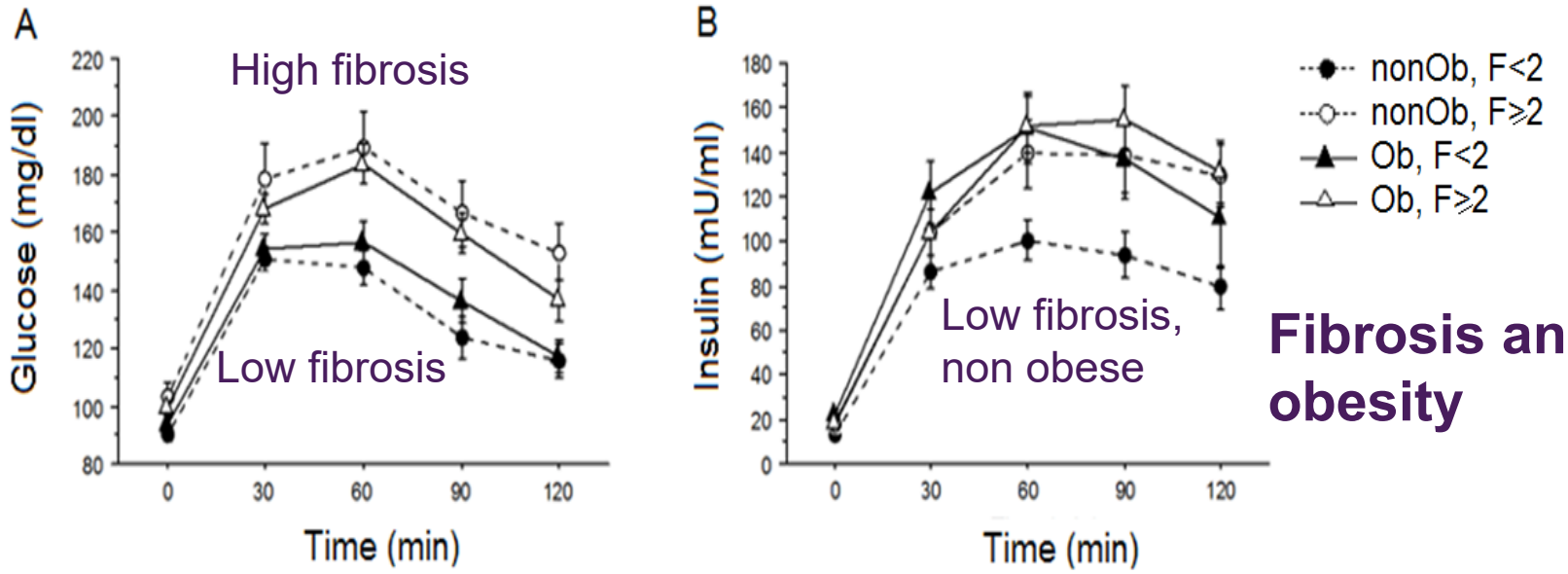


Transcriptomics



Sabatini et Cell Reports in Medicine 2024

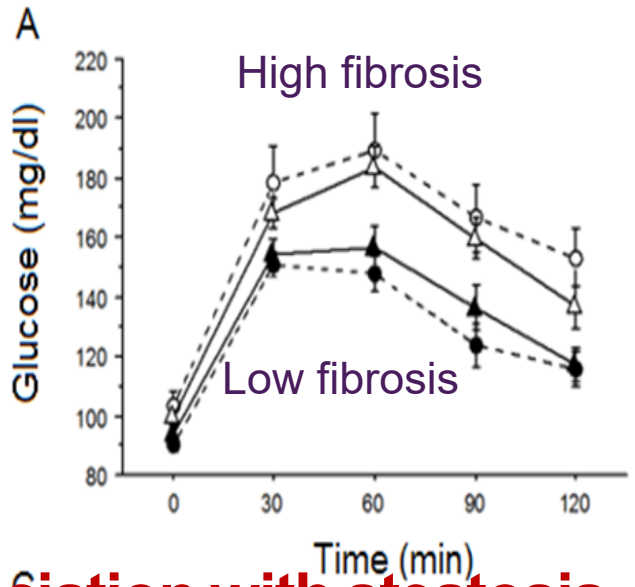
Glucose and Insulin are higher in subjects with MASLD and Fibrosis >=2 independent of obesity

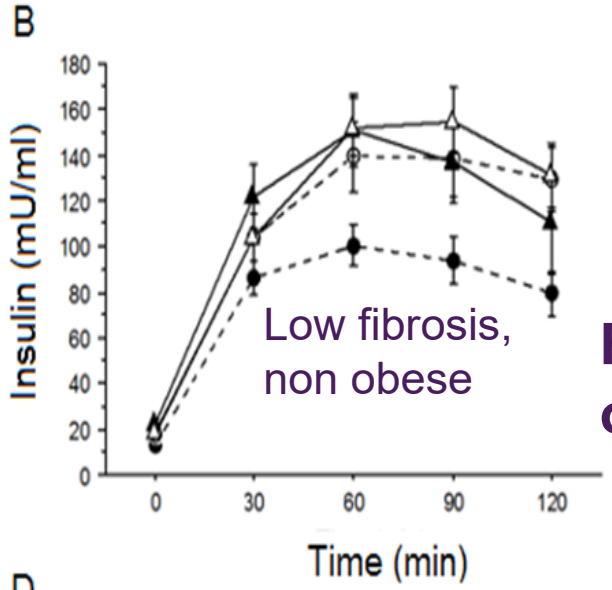


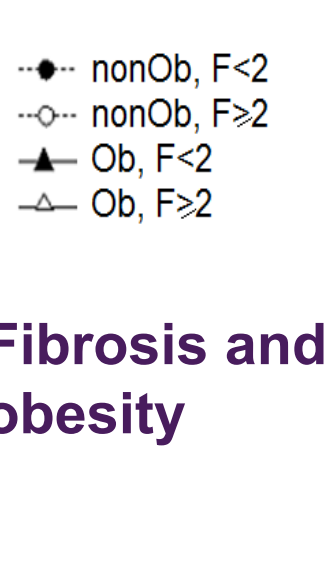
Fibrosis and obesity

Muscle insulin resistance was evaluated by OGTT with the measurement of OGIS index

Glucose and Insulin are higher in subjects with MASLD and Fibrosis >=2 independent of obesity

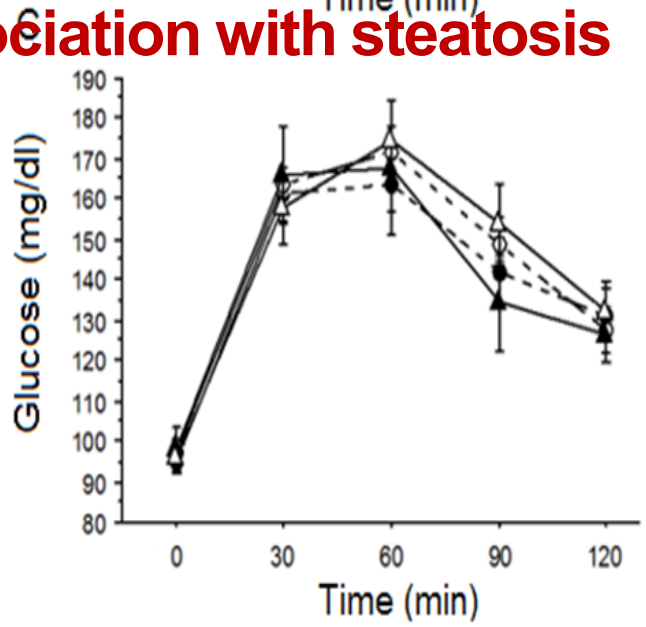


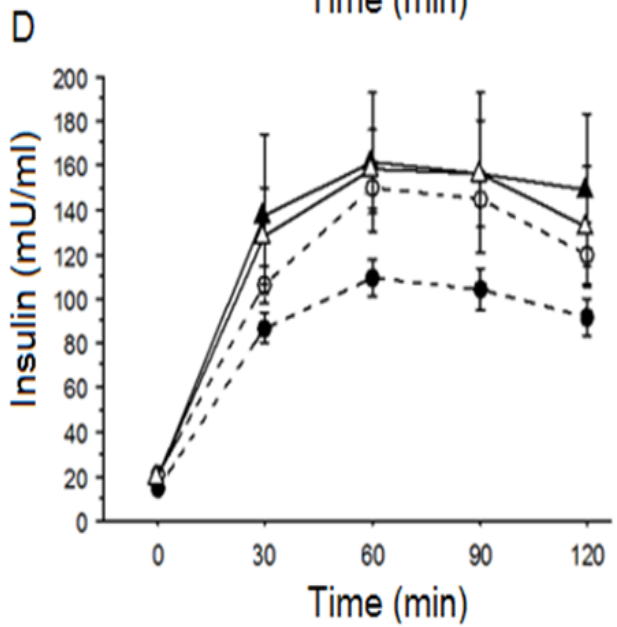


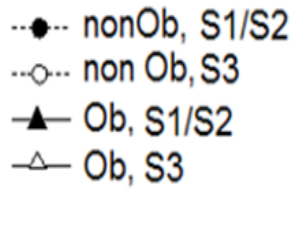


Fibrosis and obesity

No association with steatosis

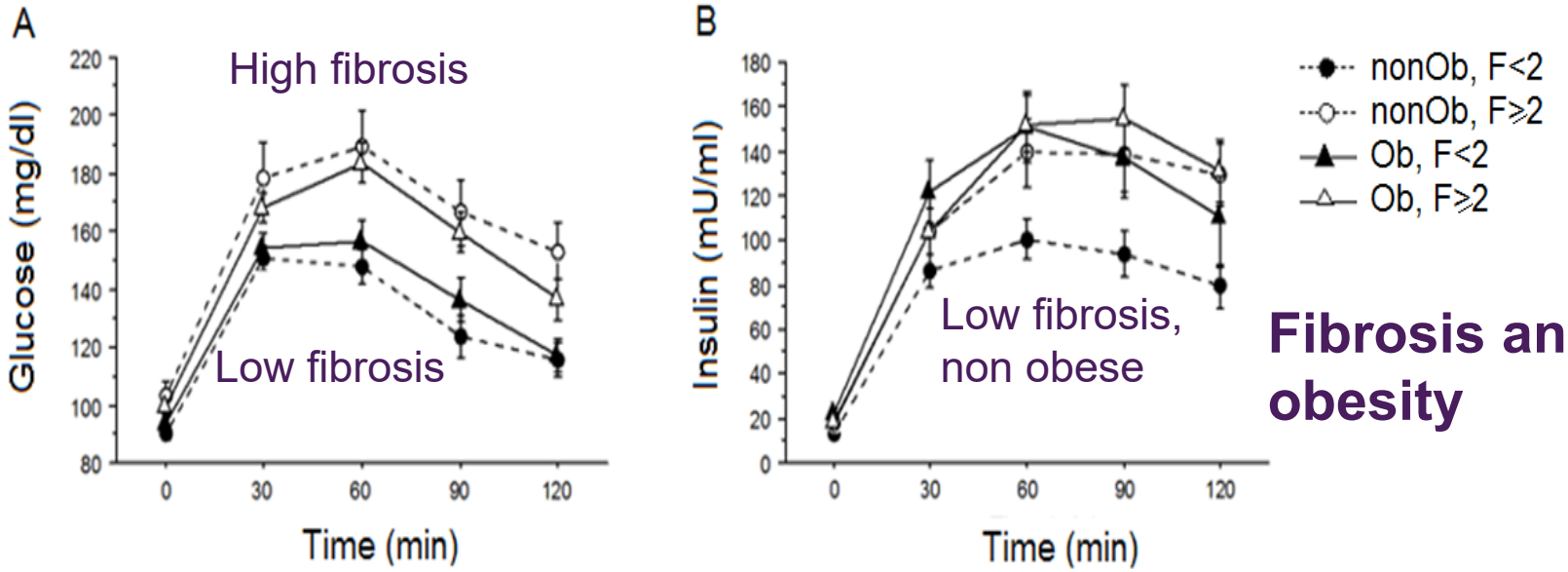






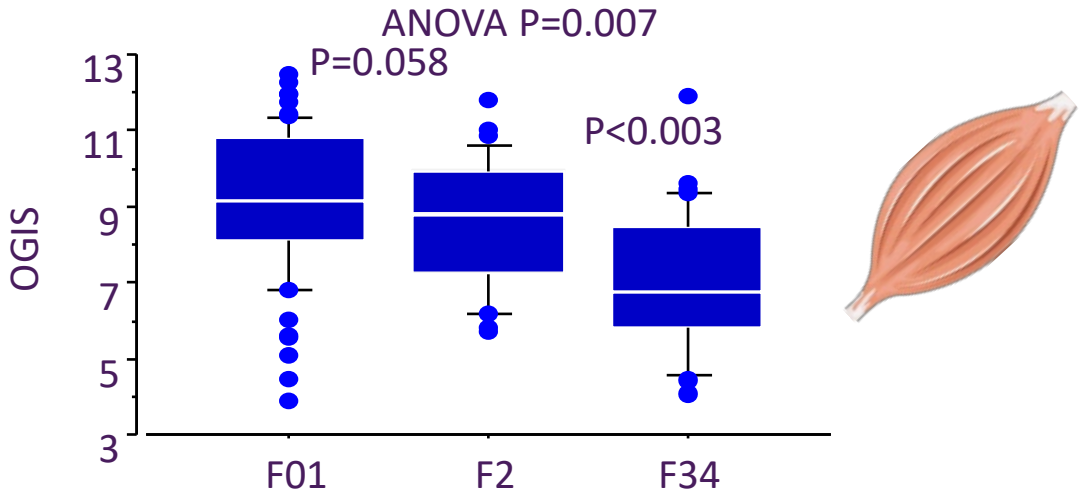
Steatosis and obesity

Glucose and Insulin are higher in subjects with MASLD and Fibrosis >=2 because of higher insulin resistance not reduced insulin secretion

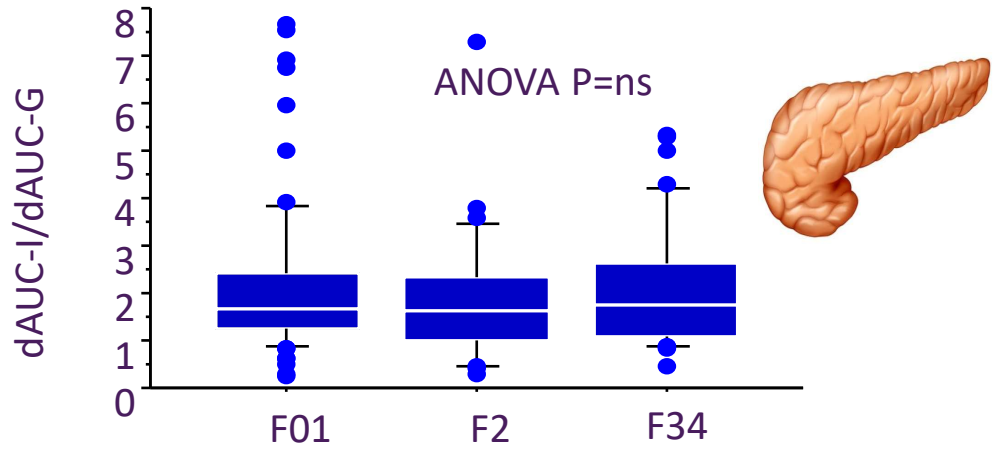


Fibrosis and obesity

Insulin sensitivity decreases with fibrosis



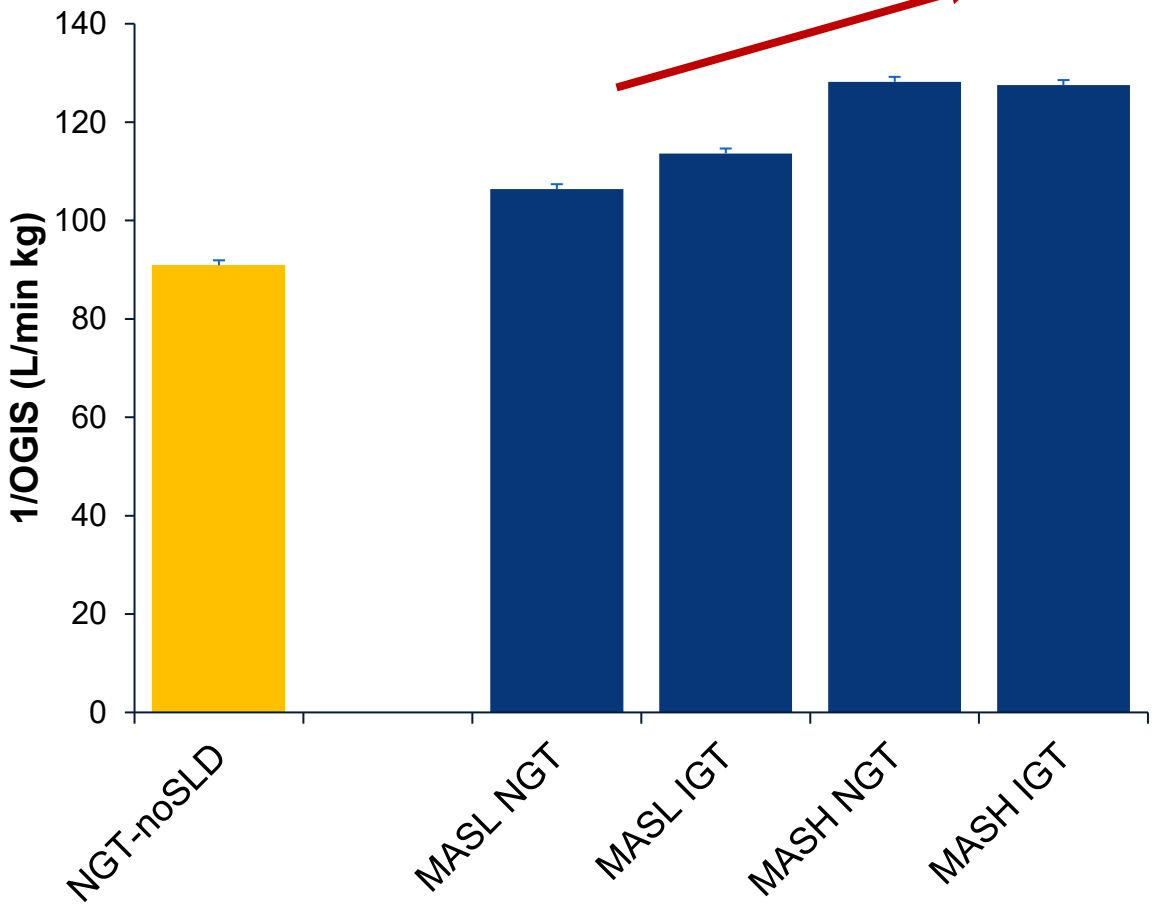
Insulin response



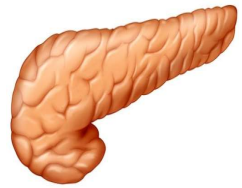
OGTT and worsen with MASH

OGTT hyperglycemia is due to ↑IR and ↓ insulin release during

↑INSULIN RESISTANCE

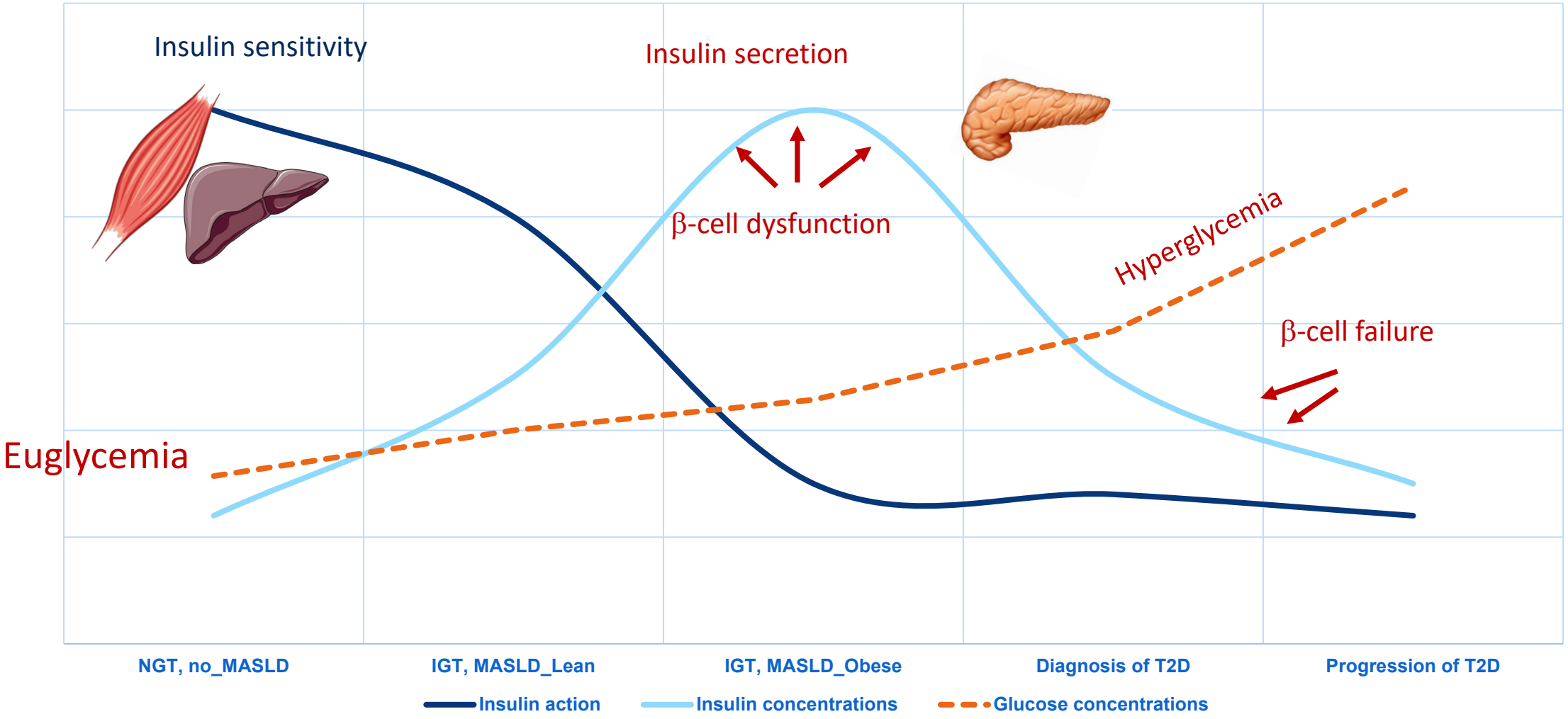


↓ GLUCOSE STIMULATED INSULIN RELEASE



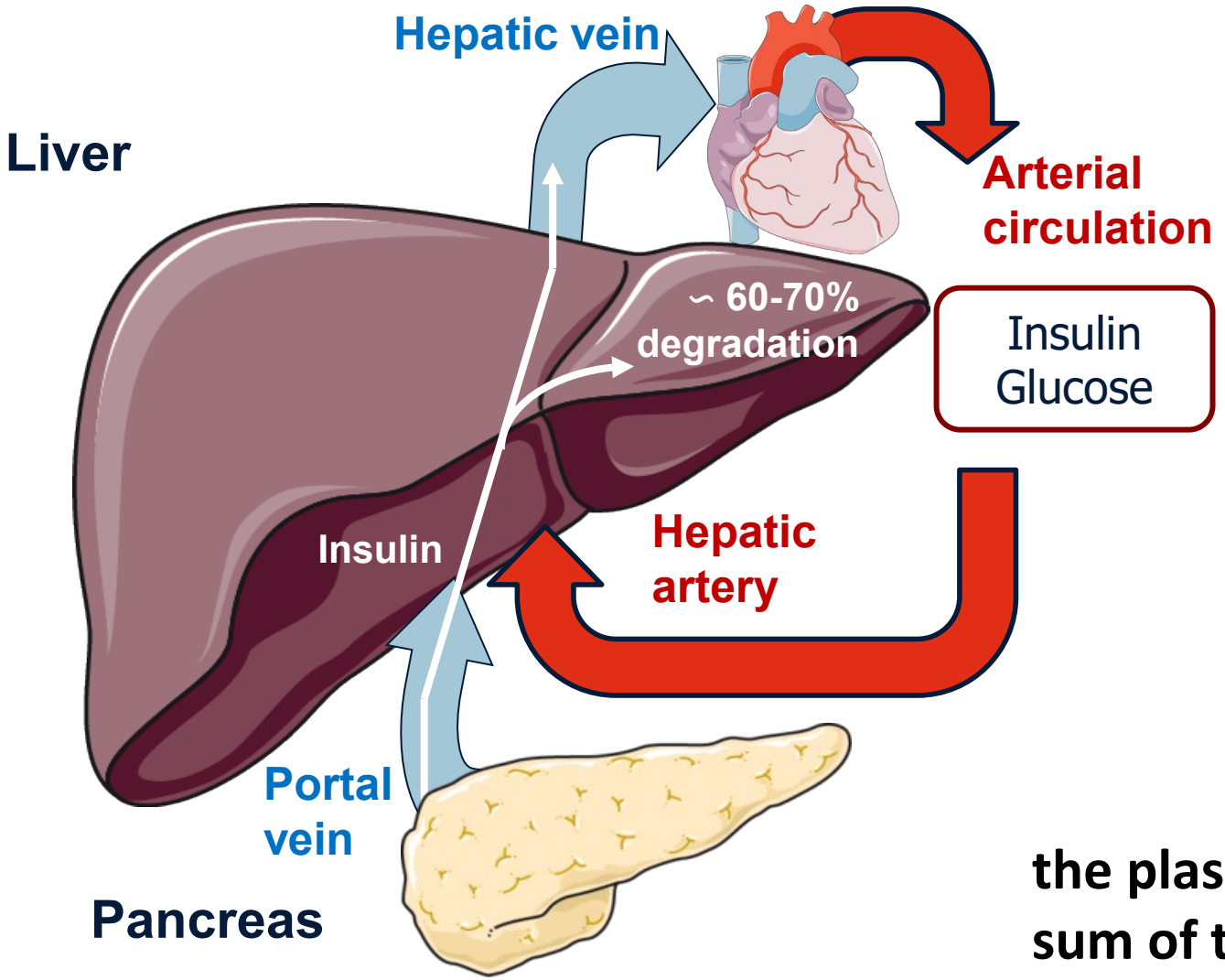
Alterations in Glucose Metabolism in MASLD

Individuals with MASLD have increased insulin resistance in liver, muscles, and adipose tissue, even if they do not have obesity and/or diabetes. ↑**Risk of T2D**



Gastaldelli, Cusi, JHEP Rep. 2019

Liver-pancreas cross-talk



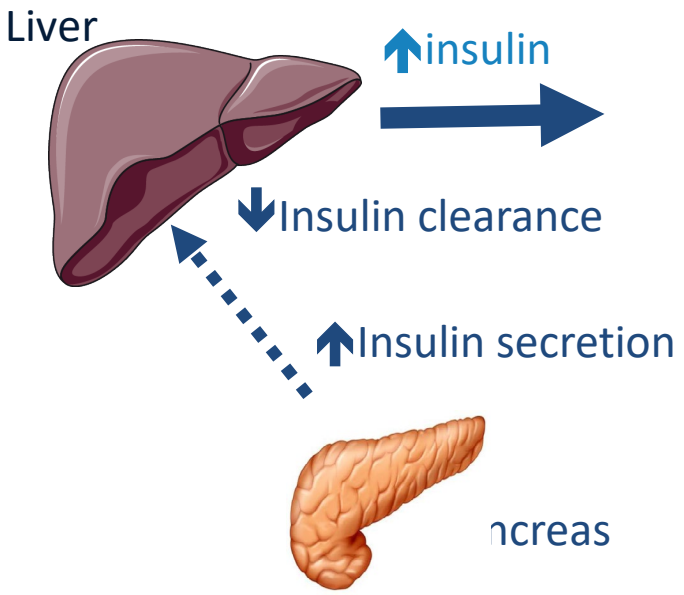
The cross talk pancreas- liver is very important for both hepatic and peripheral metabolism

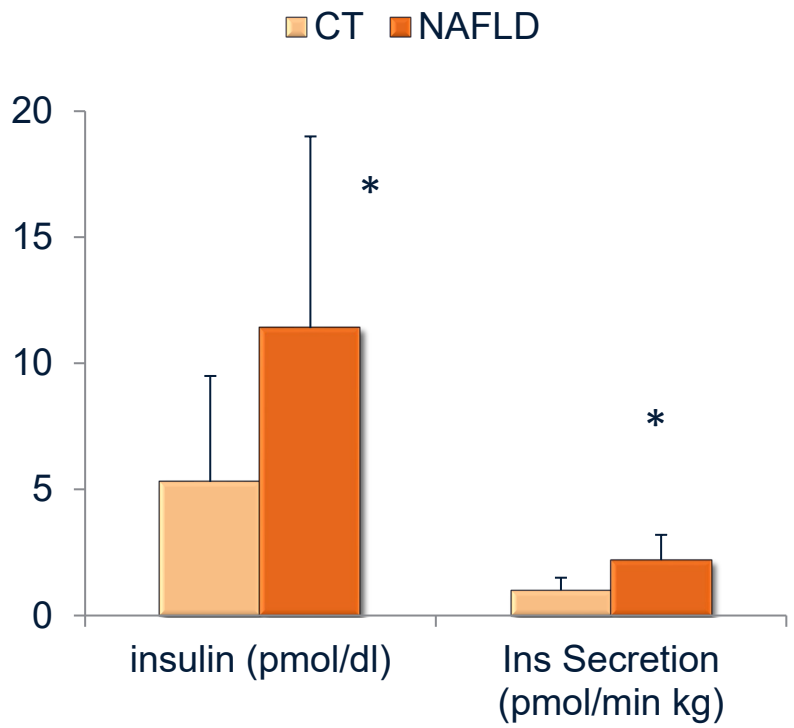
Disruption in liver-pancreas cross talk

↑Risk of T2DM

the plasma insulin response represents the sum of the beta cell insulin secretory rate and the insulin clearance (mainly hepatic)

MASLD patients have higher fasting insulin because of high ISR and reduced ins clearance

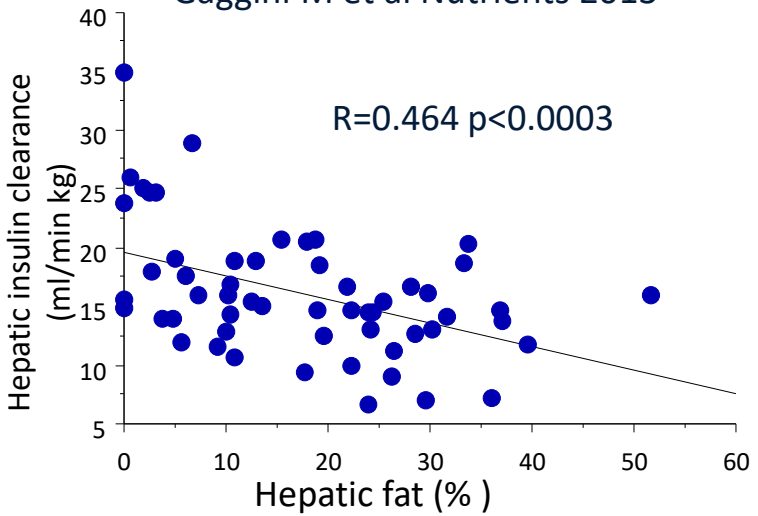


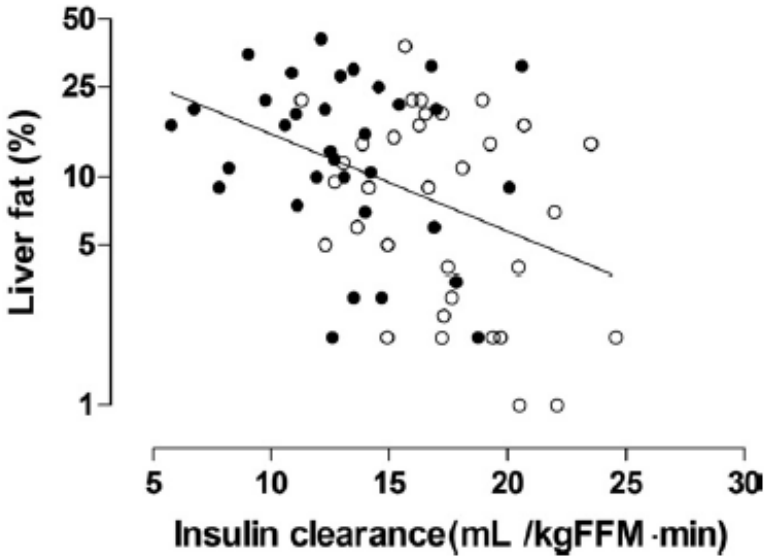


Data are presented as median± interquartile range

Junker et al J Hepatol 2016

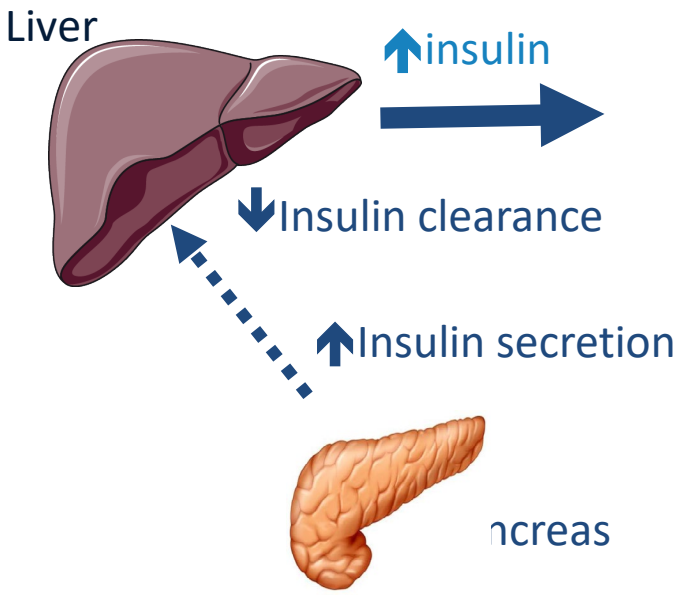
Gastaldelli Cusi Gastroenterology 2007, Gaggini M et al Nutrients 2013

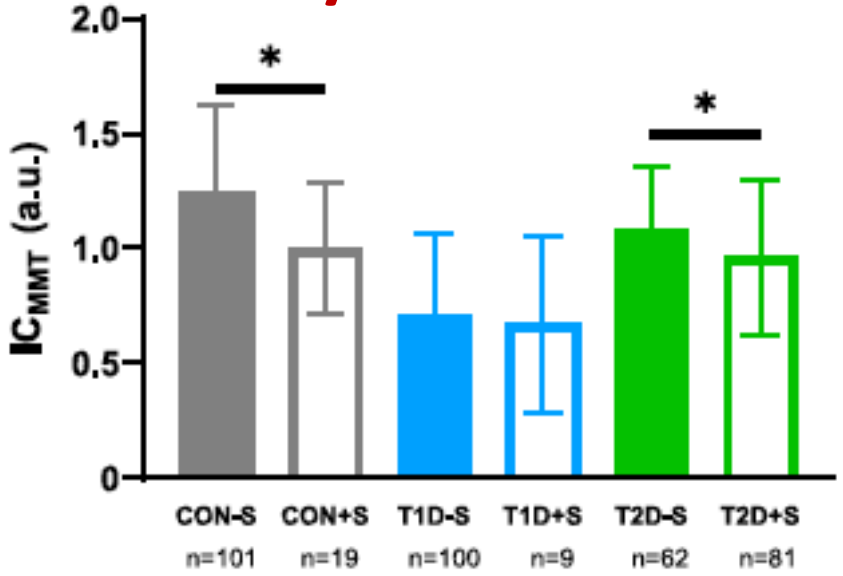




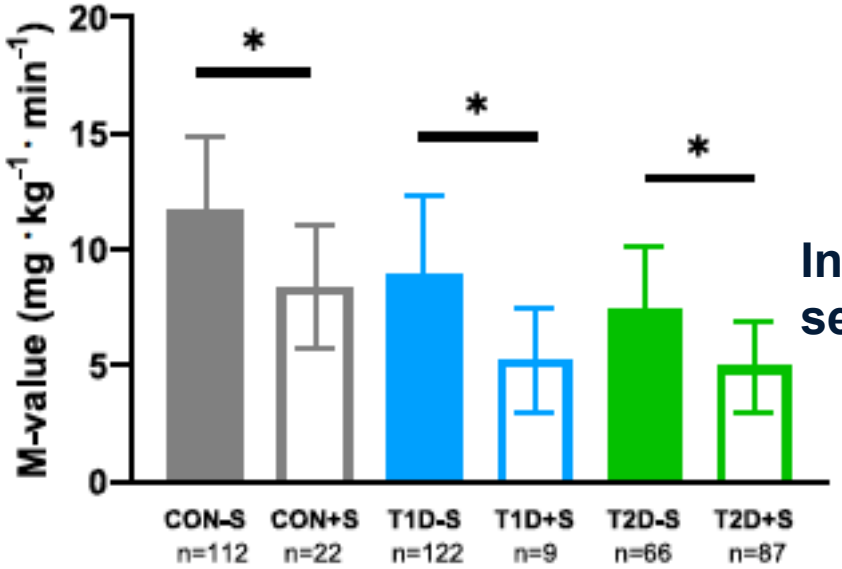
Kotronen Gastroenterology 2008

Impact of hepatic steatosis on whole-body insulin sensitivity and insulin clearance in patients with/without diabetes



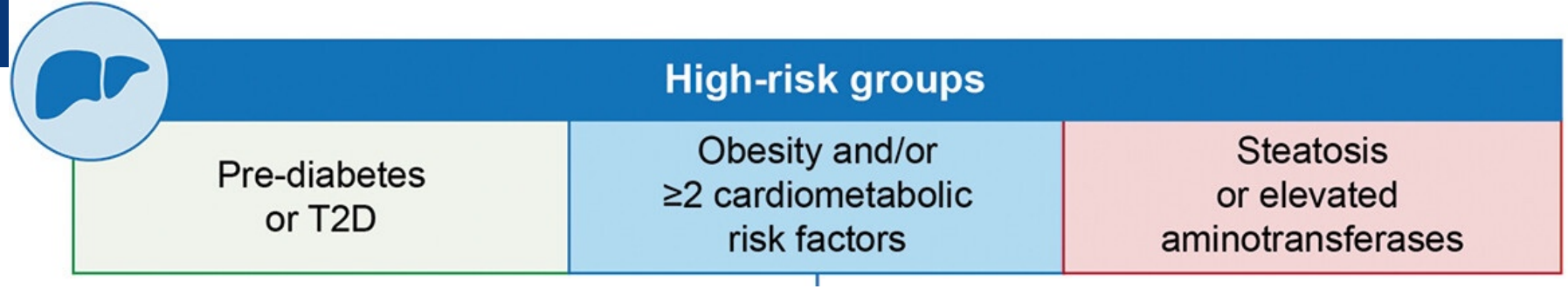


Insulin clearance



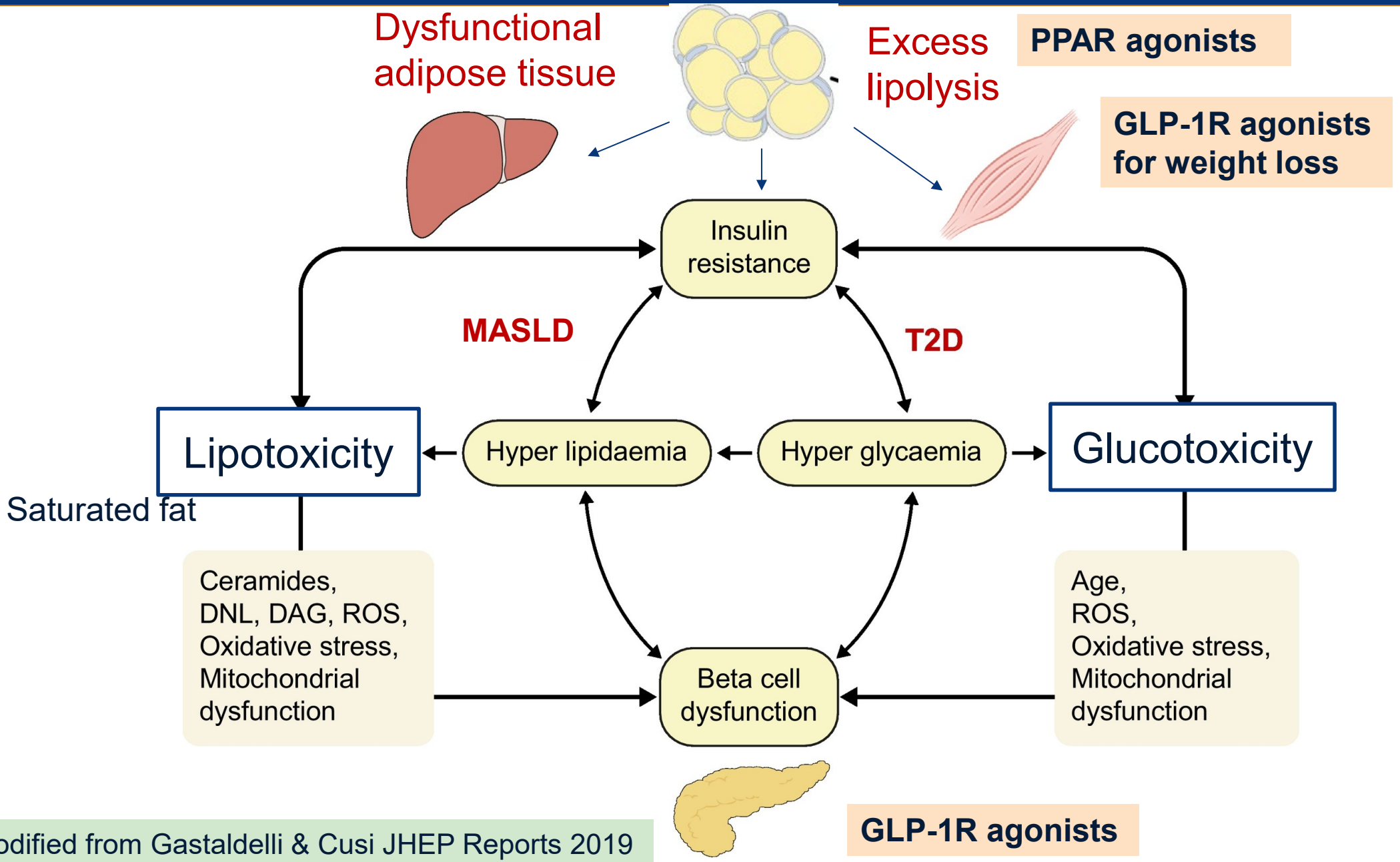
Insulin sensitivity

Treatment



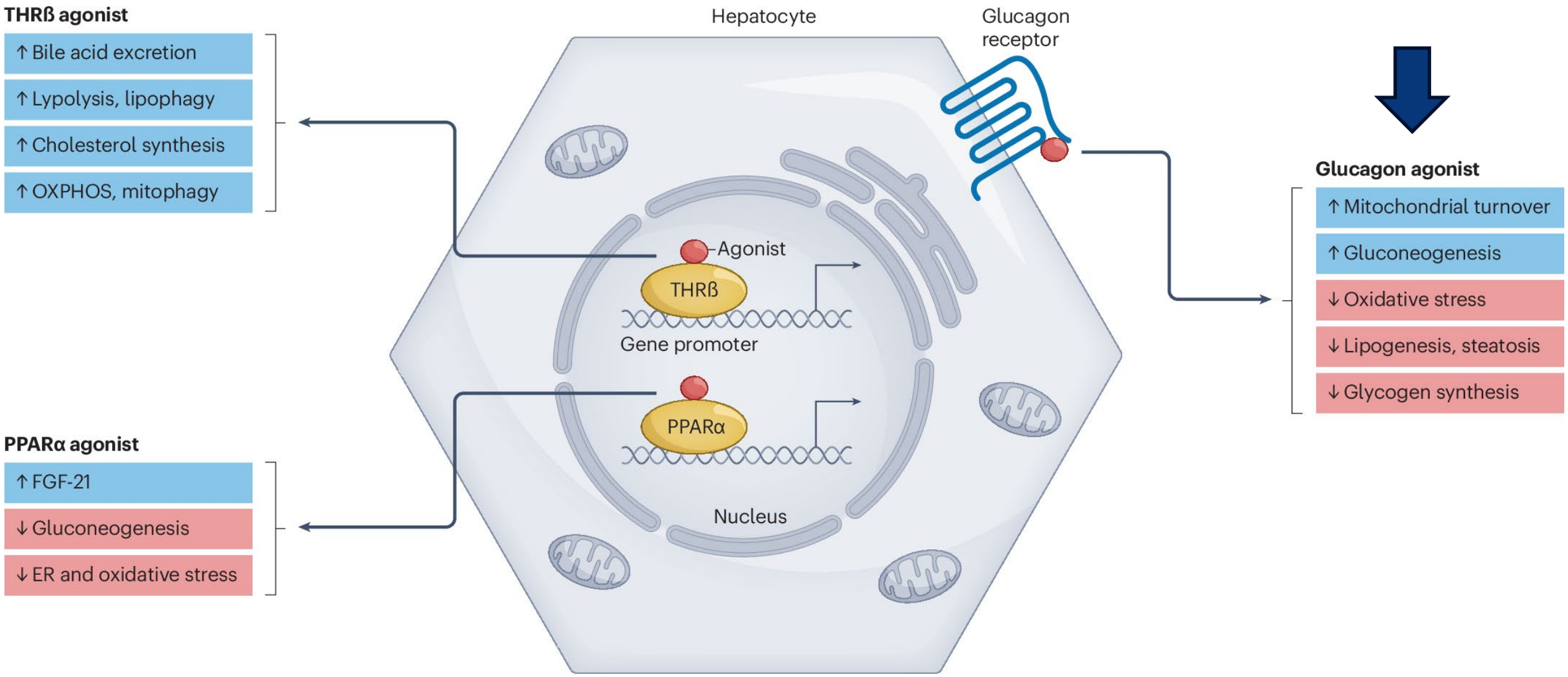
From Gastaldelli&Newsome JCEM 2025, EASL-EASD-EASO CPG J Hepatol 2024

Strong link between MASLD and T2D



Modified from Gastaldelli & Cusi JHEP Reports 2019

Only THRβ, PPARα and glucagon agonists act on hepatocytes



Do et al Nature Reviews Drug Discovery (2024)

Intervention for resolution of MASH and impact of weight loss

Diet and lifestyle intervention 1 year

Bariatric surgery 1 year

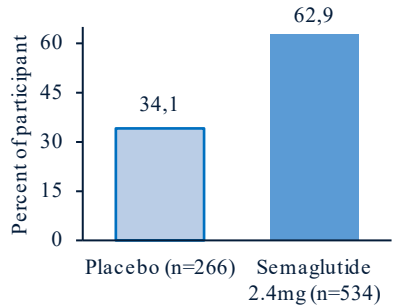
GLP-1 agonists

Semaglutide 0.4mg daily for 72w

Tirzepatide 5-15mg weekly for 52w

Survodutide 2.4-6.0mg weekly for 48w

Semaglutide 2,4mg weekly for 72w



Pioglitazone, 45 mg/d for 18 months

Lanifibranor 800-1200mg daily for 52w

Resmetirom 80-100mg daily for 52w

F Carli et al JHep Reports 2024

Conclusions

Abnormal glucose metabolism in MASH even in those without T2D, and associated to hepatic inflammation and fibrosis (not steatosis)

In MASLD it is important to improve both glucose and lipid metabolism and to improve IR, in particular in adipose tissue and liver.

Weight loss is the most effective way to resolve MASLD, although not all drugs work through weight loss

National Research Council of Italy

MASLD Study Group

EGIR European Group for the study of Insulin Resistance

Study Groups

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LITMUS

EU Horizon 2020 IMI-2 under grant agreement No. 777377

SOPHIA Stratification of Obese Phenotypes to Optimize Future Obesity Therapy

EU Horizon 2020 IMI-2 under grant agreement No. 875534

PAS GRAS

Horizon Europe under grant agreement No. 101080329

FoieGras

EU Horizon 2020 Marie Skłodowska-Curie grant agreement No 722619.

EPoS Elucidating Pathways of Steatohepatitis

EU Horizon 2020 under grant agreement No. 634413

GRIPonMASH

Horizon Europe IHI-JU under grant agreement No. 101132946

Horizon Europe