Pathophysiological relationship between MASLD and T2D

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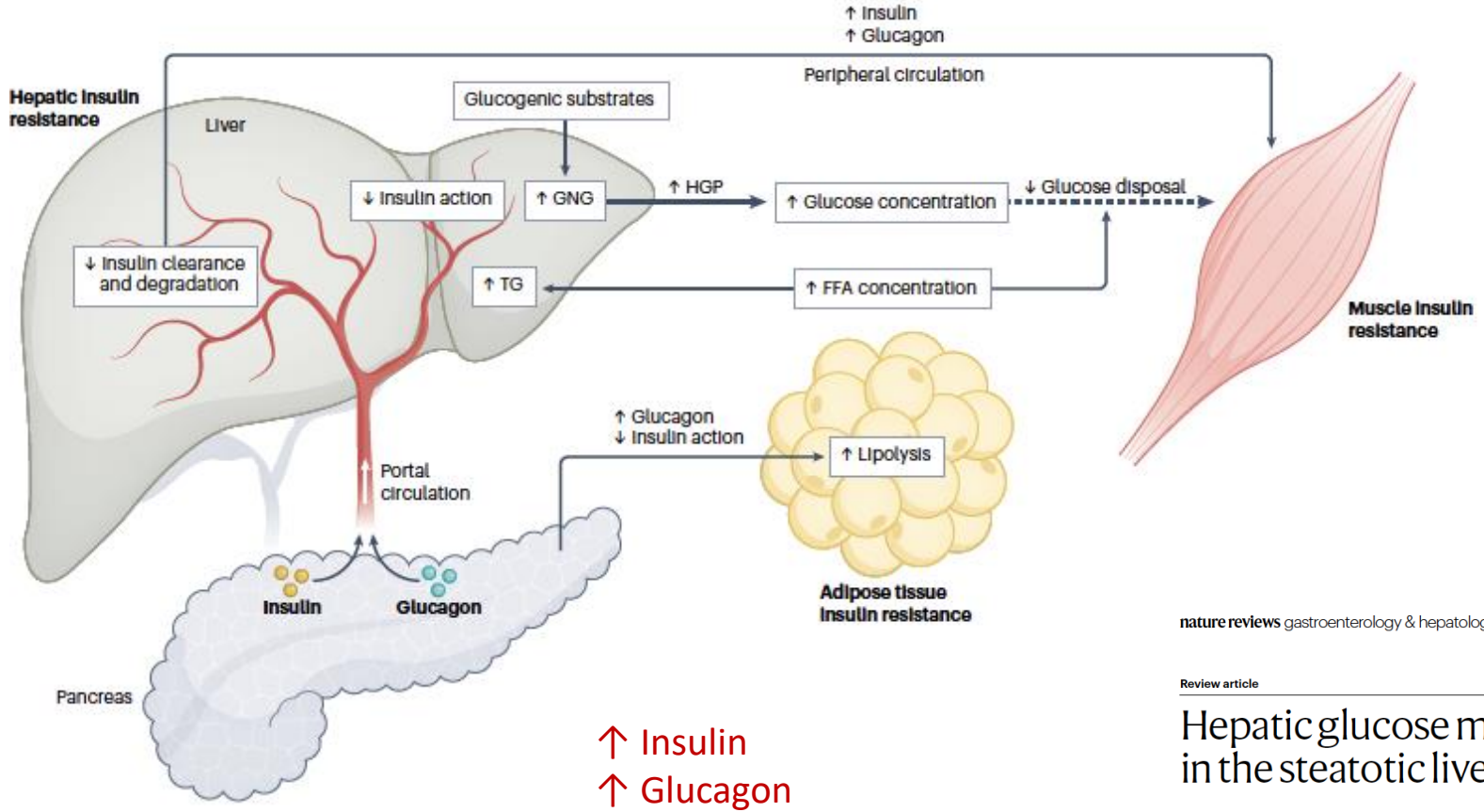
Conflict of interest

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 and Pfizer

Not only lipid but also glucose metabolism is altered in MASLD



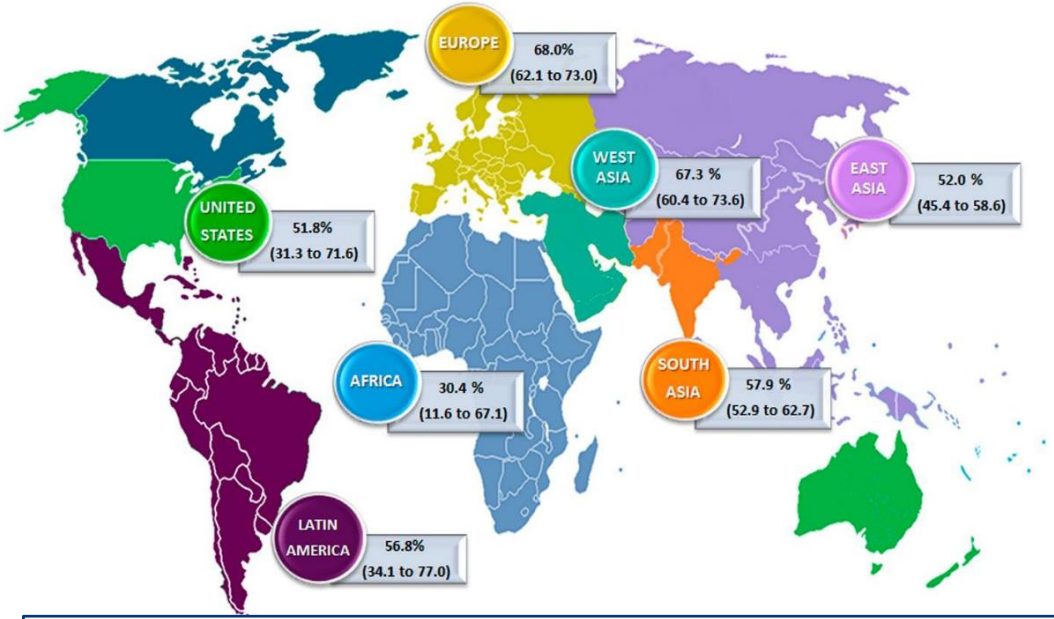
↑ Insulin
↑ Glucagon

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]

Strong correlation between MASLD and 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

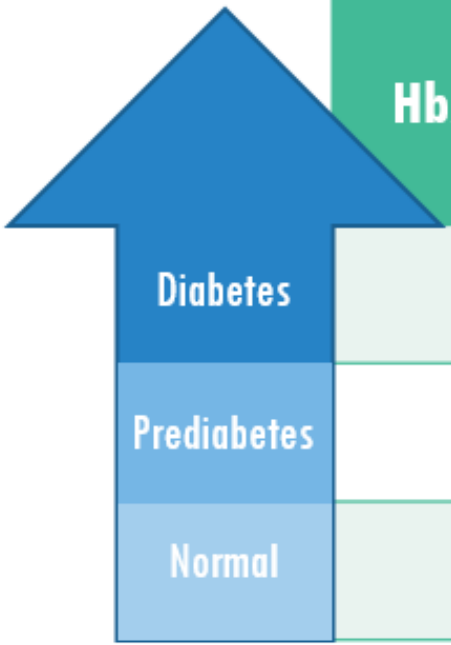
2045 68 million
2030 66 million
2019 59 million
15% increase

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**

Both fasting and postprandial hyperglycemia in T2D



	HbA1c (percent)	Fasting Plasma Glucose (mg/dL)	Oral Glucose Tolerance Test (mg/dL)
Diabetes	≥ 6.5	≥ 126	≥ 200
Prediabetes	5.7 – 6.4	100 - 125	140 – 199
Normal	~ 5.7	≤ 99	≤ 139

Source: adapted from American Diabetes Association (2012)

MASLD and T2D

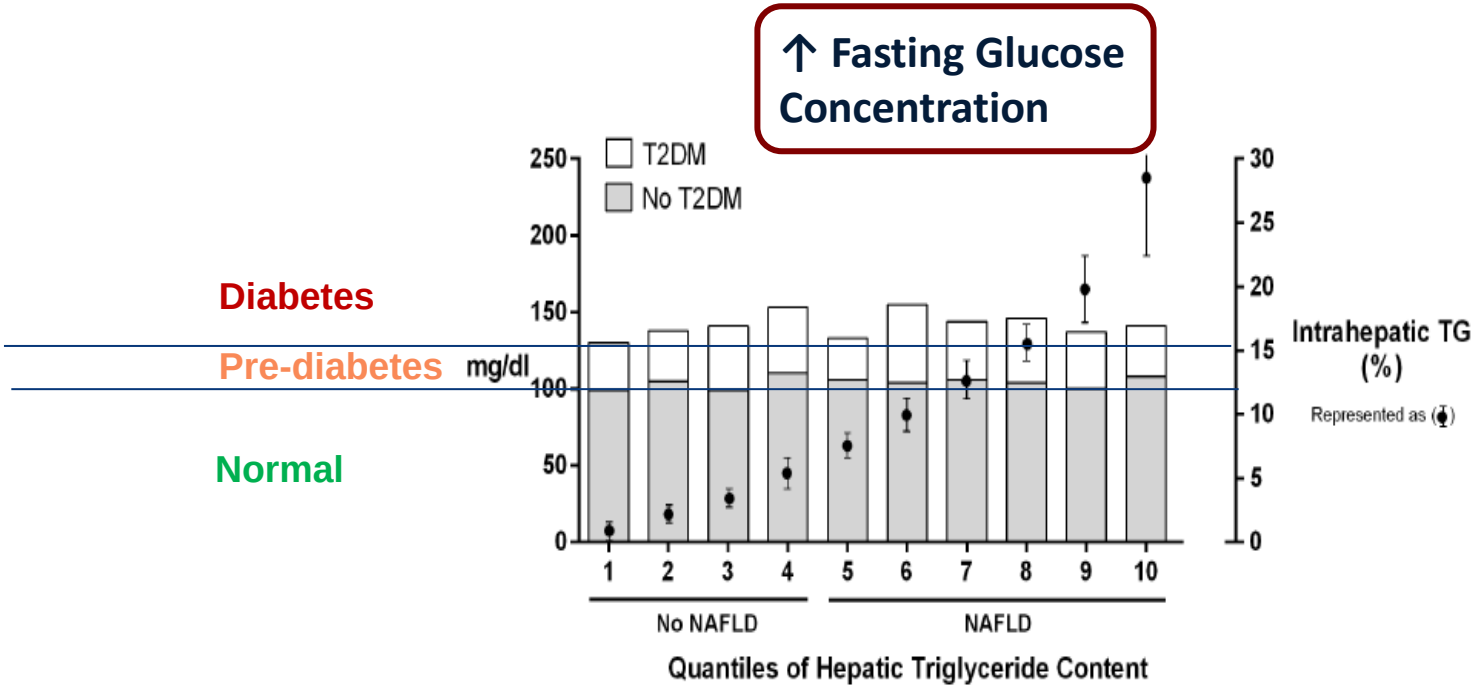
- Fasting glucose metabolism
- Postprandial glucose metabolism

MASLD and T2D

- **Fasting glucose metabolism**
- **Postprandial glucose metabolism**

MASLD have high fasting glucose

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



Why MASLD have high fasting glucose

Hepatic Insulin Resistance

High EGP and gluconeogenesis

Peripheral insulin

Muscle Insulin Resistance

↓ Glucose disposal

↑EGP

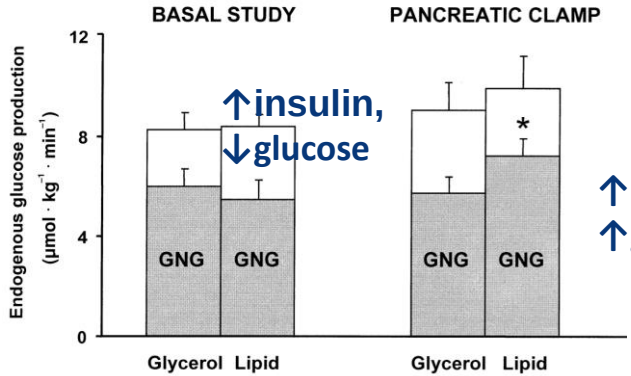
↑ Fasting Glucose Concentration

X

Insufficient glucose disposal

FFA

AT Insulin Resistance

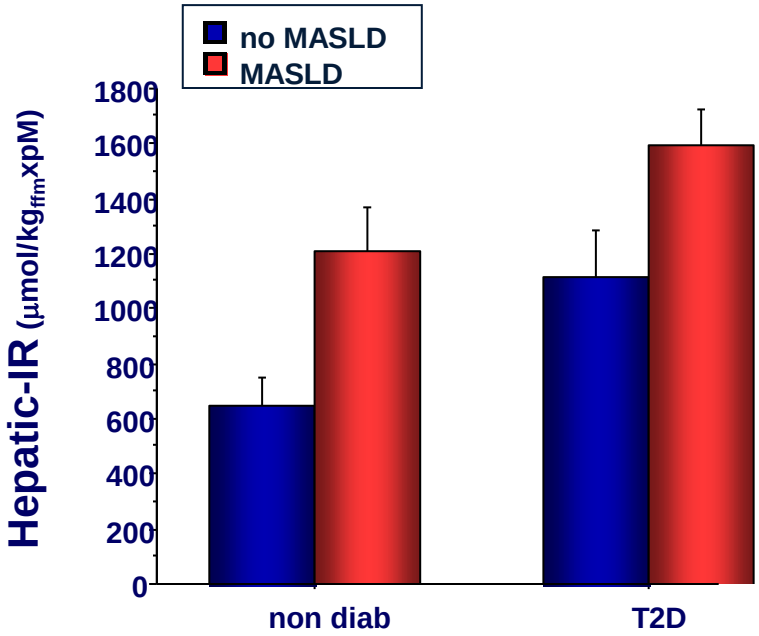


↑insulin, ↓glucose

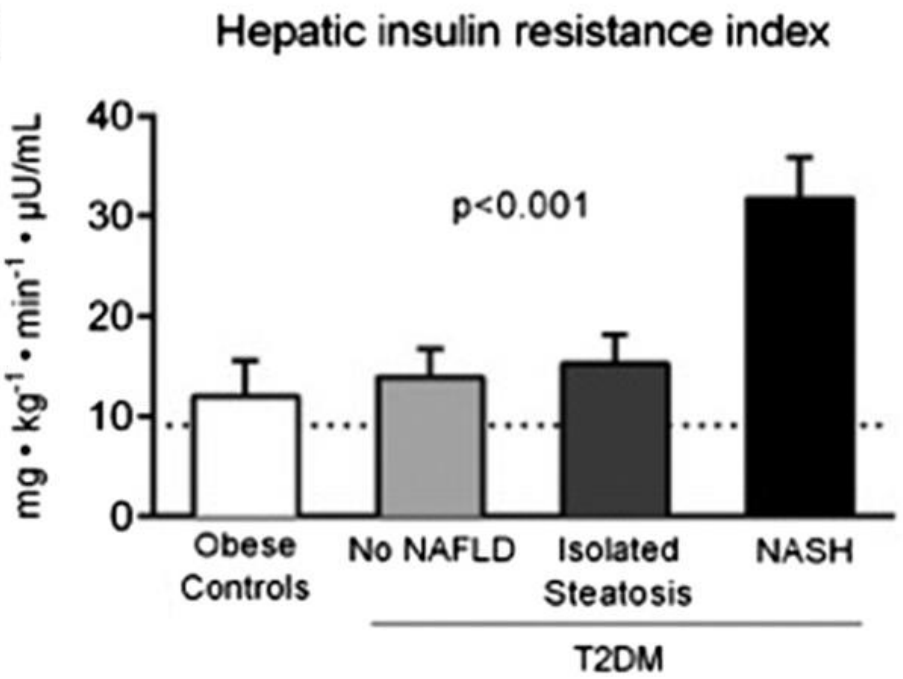
↑GNG, ↑glucose

Roden, Diabetes 2000

Fasting hepatic insulin resistance is increased in MALSD and even more in T2D



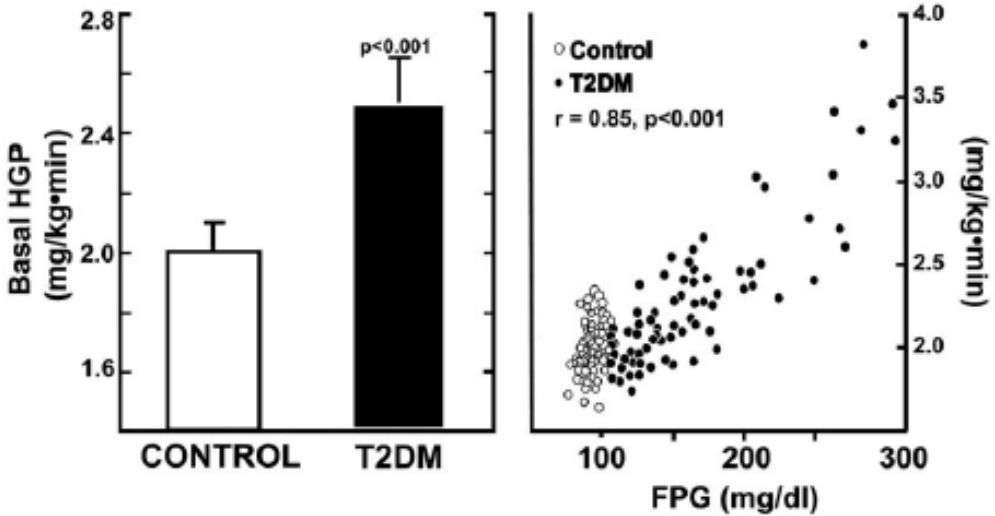
Gastaldelli et al Gastroenterology 2007



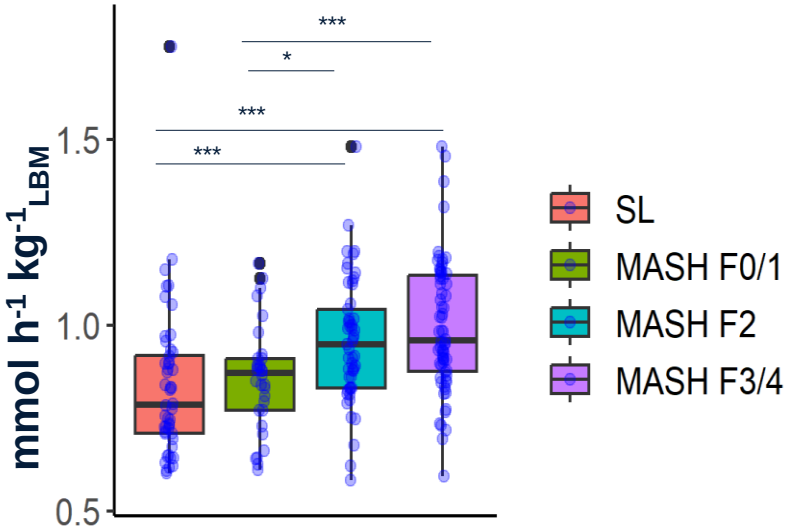
Lomonaco Diabetes Care 2016

EGP is increased in T2D and in MASH with fibrosis (even without T2D

High EGP and gluconeogenesis have been shown to explain high fasting glucose



DeFronzo Diabetes 2009



Unpublished data, Subjects without diabetes

MASH have higher fasting EGP and Hep-IR

Hepatic Insulin Resistance

Impaired suppression of EGP

Peripheral insulin

Muscle Insulin Resistance

Insulin clearance

EGP

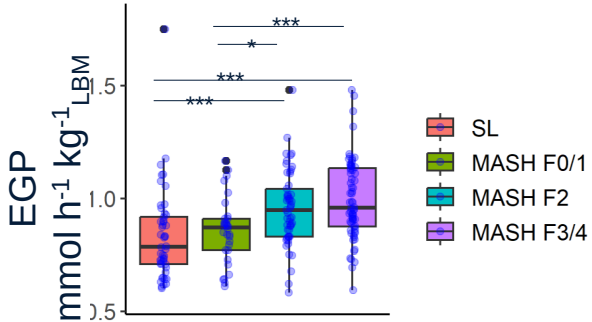
↑ Fasting Glucose Concentration

↓ Glucose disposal

Insufficient glucose disposal

FFA

AT Insulin Resistance

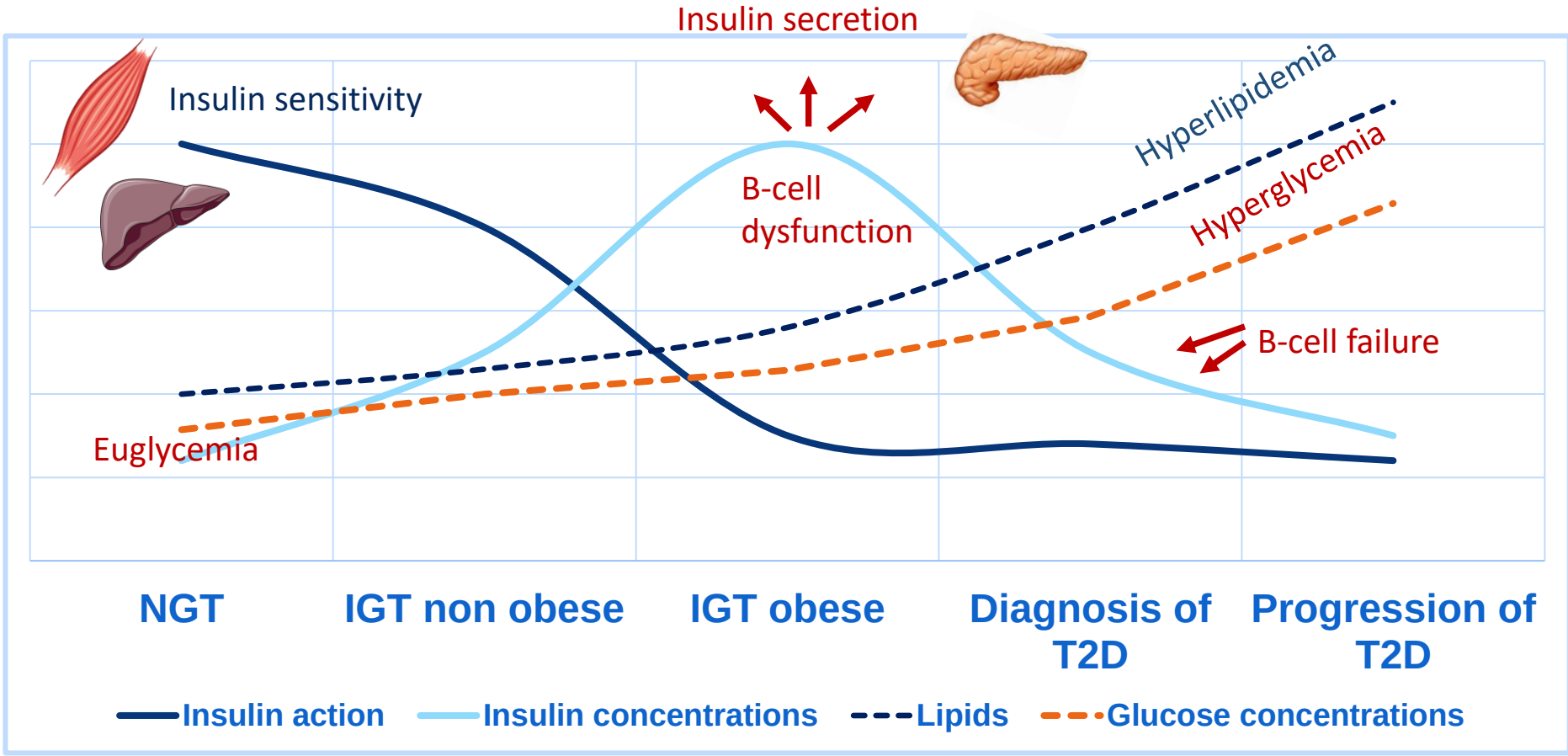


↑ EGP and Hep-IR are the defects Associated to high FPG in MASLD

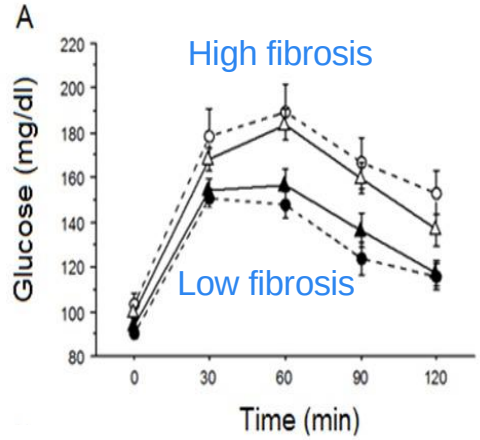
MASLD and T2D

- Fasting glucose metabolism
- **Postprandial glucose metabolism**

IR and impaired postprandial insulin secretion ↑Risk of T2D

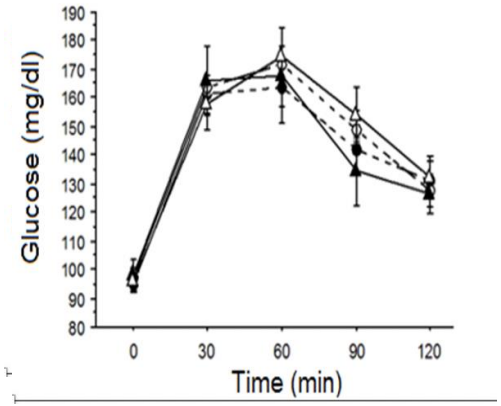


OGTT hyperglycemia in severe fibrosis, not steatosis



Fibrosis (w/wo obesity) is associated to higher glucose

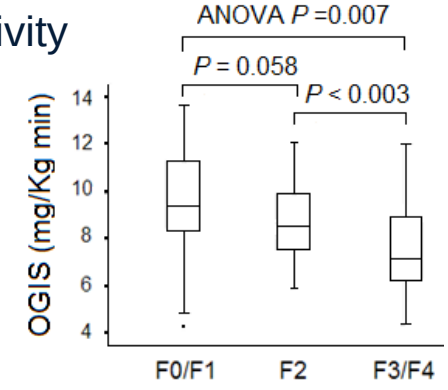
n=139	NASH
M/F	112/17
Age	43 ± 10
BMI	27 ± 5
NW/Ow/Ob (%)	12/63/25
S1+S2/S3 (n)	76/63
F01/F2/F34 (n)	71/34/34



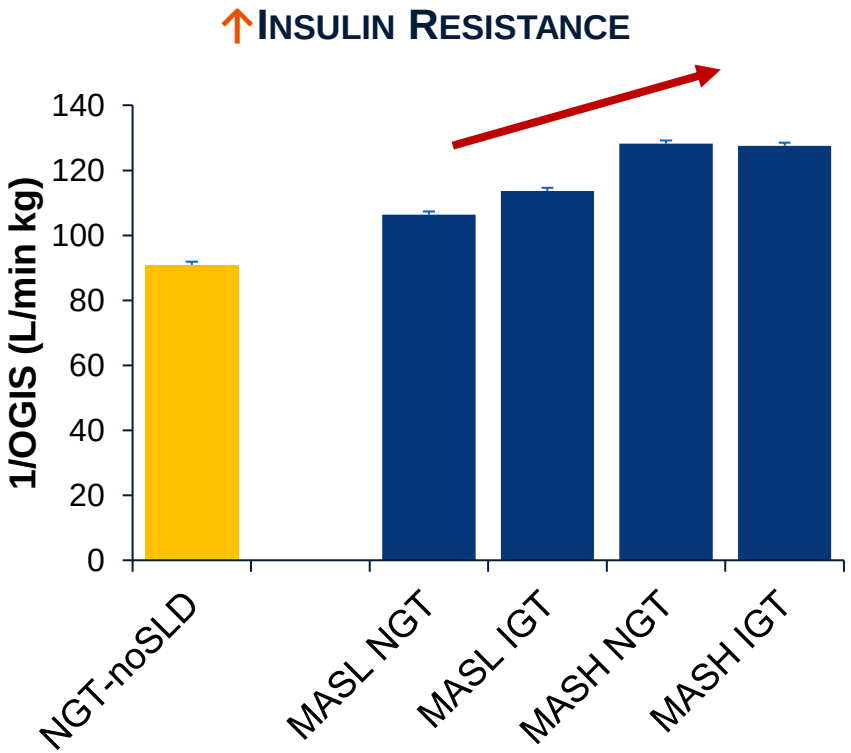
No effect of steatosis or obesity

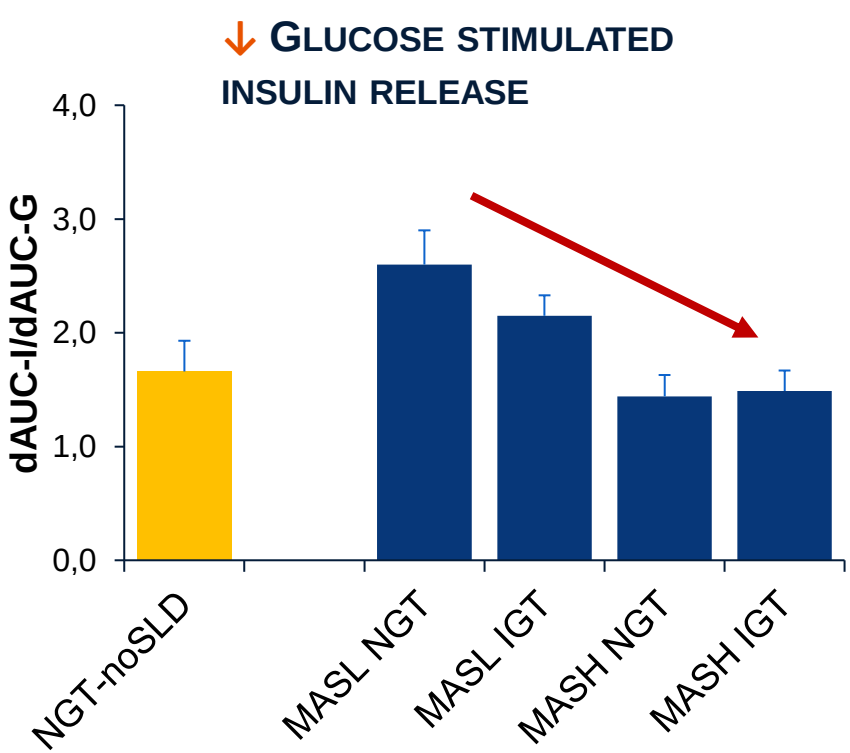
Glucose response to OGTT is higher in subjects with Fibrosis >=2, while steatosis grade makes a minor impact

↓insulin sensitivity



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





Postprandial hyperglycemia in MASLD

Hepatic Insulin Resistance

Impaired suppression of EGP

Peripheral insulin

Muscle Insulin Resistance

↑EGP

↓ Insulin clearance

↑↑ Glucose Concentration

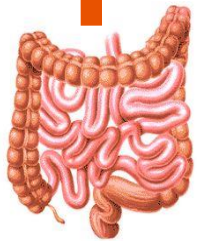
↓Glucose disposal

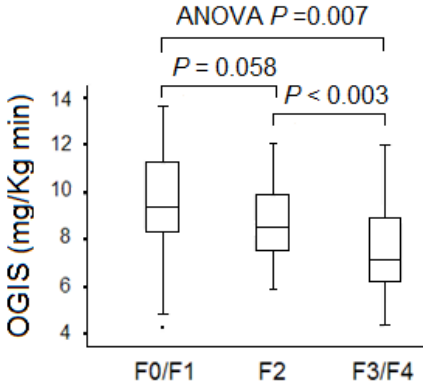
X

Insufficient glucose disposal

Portal insulin

↓ Insulin secretion

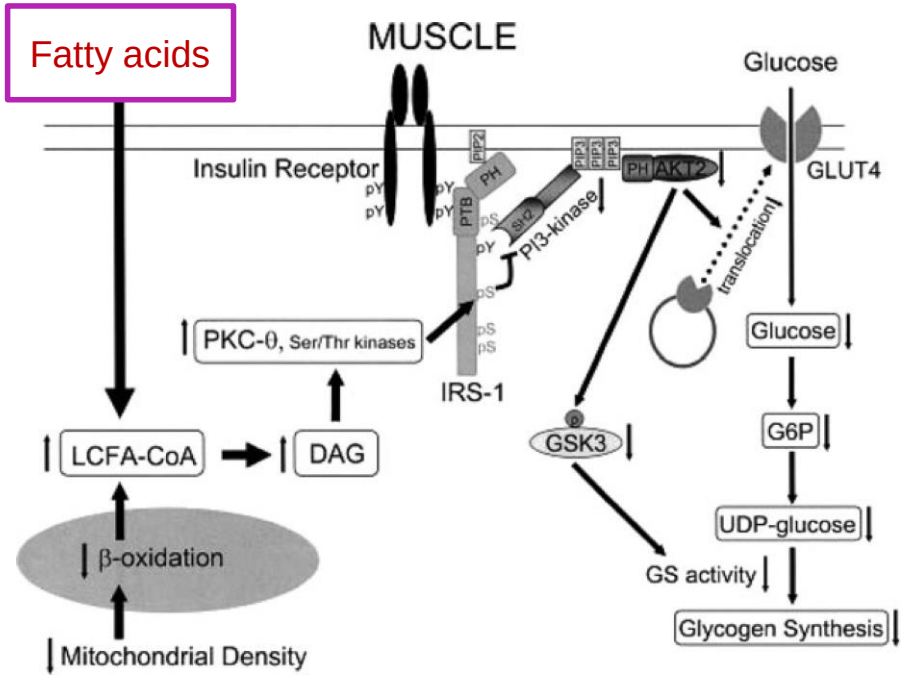




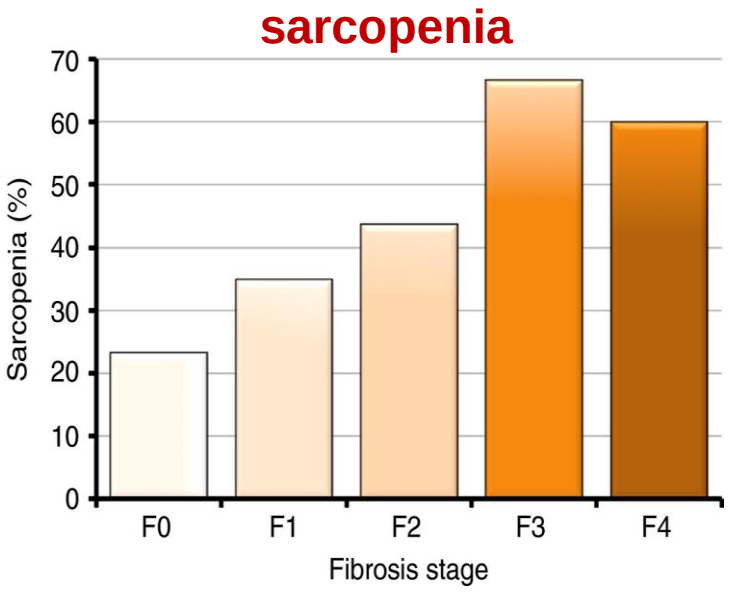
Muscle-IR and impaired insulin secretion are the main determinants of ↑postprandial glucose in MASH with fibrosis

WHY MUSCLE IR and reduced glucose disposal?

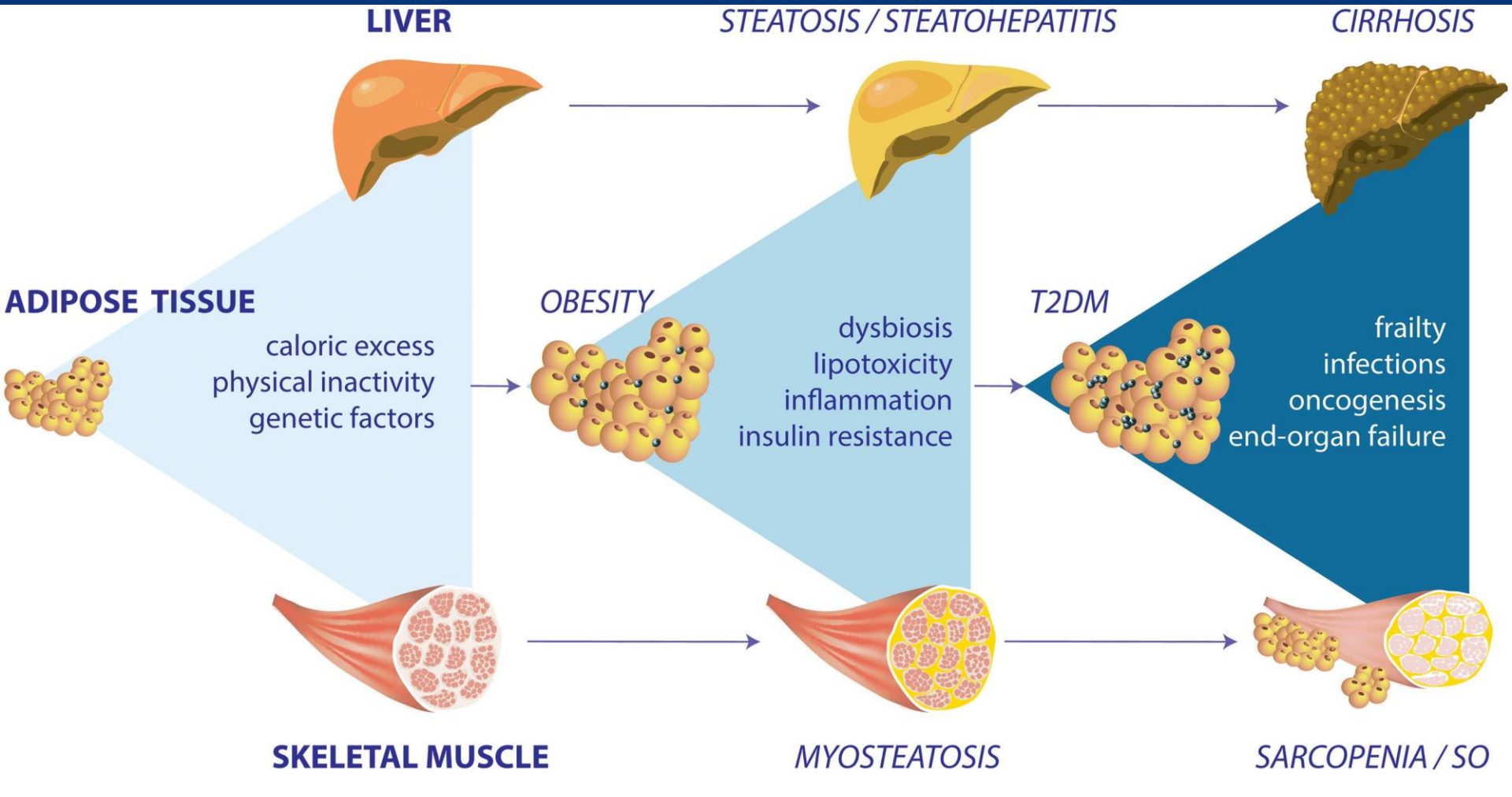
- Reduced phosphorylation of insulin genes
- Myosteatosis
- Reduced muscle mass (sarcopenia)



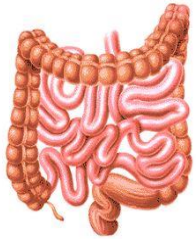
Jornayvaz, Samuel and Shulman Ann Rev Nutr 2010

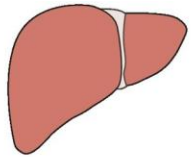


Petta et al APT 510-518, 2017


LIVER
STEATOSIS / STEATOHEPATITIS
CIRRHOSIS
ADIPOSE TISSUE
caloric excess
physical inactivity
genetic factors
OBESITY
dysbiosis
lipotoxicity
inflammation
insulin resistance
T2DM
frailty
infections
oncogenesis
end-organ failure
SKELETAL MUSCLE
MYOSTEATOSIS
SARCOPENIA / SO

↑Risk of T2DM in MASH and ↑Risk of MASH in T2DM are associated with insulin resistance and impaired insulin secretion





Myosteatosis,
Sarcopenia

Insulin resistance

MASLD

T2D

Lipotoxicity

Hyper lipidaemia

Hyper glycaemia

Gluco-Lipotoxicity

Ceramides,
DNL, DAG, ROS,
Oxidative stress,
Mitochondrial dysfunction

Beta cell dysfunction

Age,
ROS,
Oxidative stress,
Mitochondrial dysfunction

Severity of fibrosis associated with worse glucose metabolism

From Gastaldelli & Cusi JHEP Reports 2019

National Research Council of Italy

NAFLD EGIR European Group for the study of Insulin Resistance

Study Groups

GROUP

- Fabrizia Carli
- Demetrio Ciociaro
- Flavia Cozzolino
- Giuseppe Della Pepa
- Simona Fenizia
- Patrizia Infelise
- Simona Manuguerra
- Filippo Pratesi
- Samantha Pezzica
- Silvia Sabatini

PAST FELLOWS

- Chiara Barbieri
- Melania Gaggini
- Sara Guerra
- Gabriele Mocciaro
- Barbara Patricio
- Maura Pettiti
- Marco Russo
- Chiara Saponaro

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

EPoS Elucidating Pathways of Steatohepatitis

EU Horizon 2020 under grant agreement No. 634413

FoieGras

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

GRIPonMASH

Horizon Europe IHI-JU under grant agreement No. 101132946

Horizon Europe