LMKaplan0@gmail.com

Beyond Glycemic Control: Bariatric Surgery and Metabolic Disease

Lee M. Kaplan, MD, PhD

Obesity Medicine Section and Dartmouth Obesity Care Center
Geisel School of Medicine at Dartmouth

LMKaplan0@gmail.com

31 August 2023

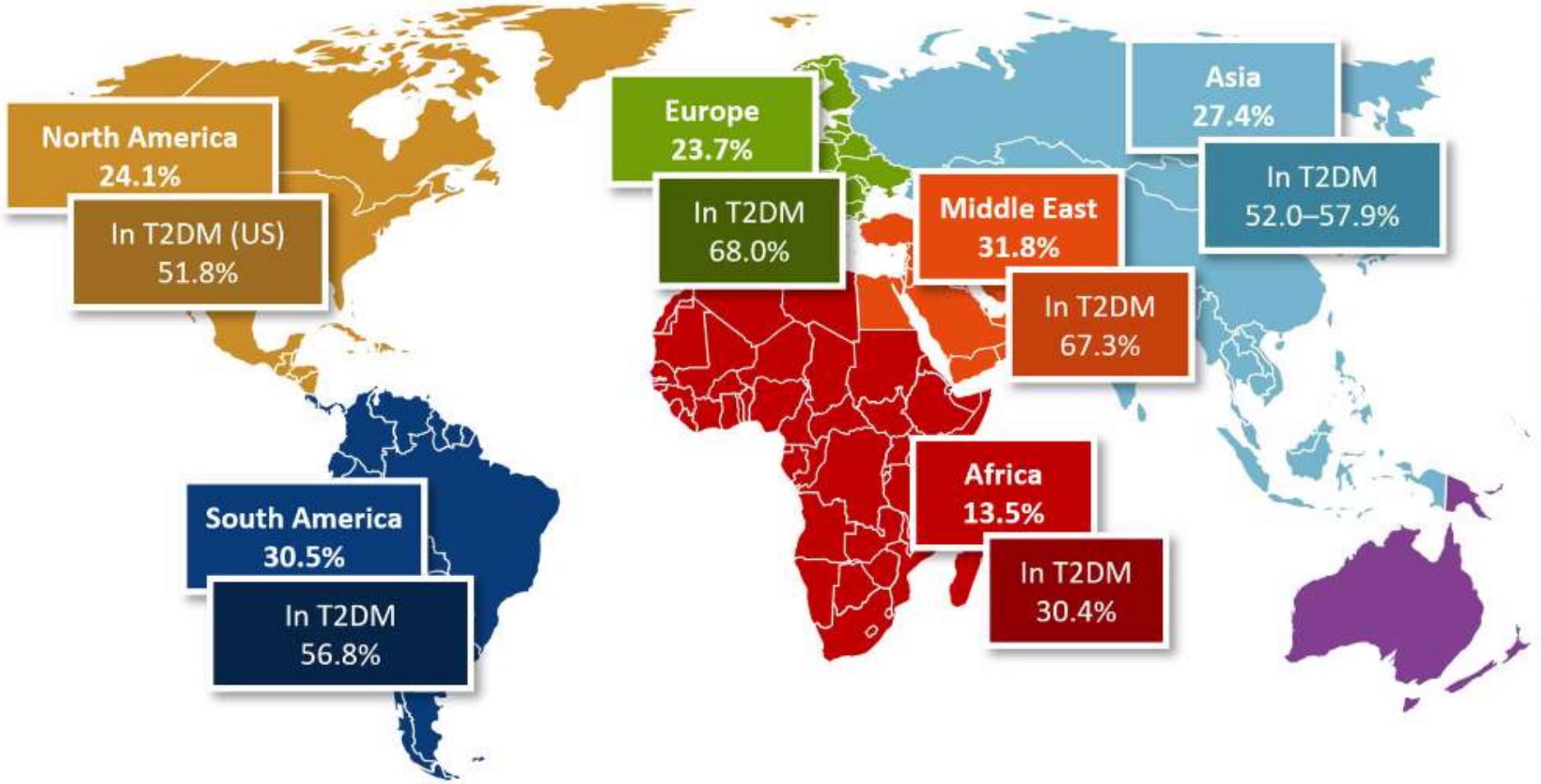
2023 IFSO World Congress

Disclosures

I am currently or have recently been a paid consultant to the following companies and organizations:

Altimmune
Amgen
Boehringer Ingelheim
Gelesis
Gilead Sciences
Eli Lilly & Company
Novo Nordisk
Pfizer
Rhythm Pharmaceuticals
Sidekick Health
The Obesity and Nutrition Institute
twenty30.health
Xeno Biosciences

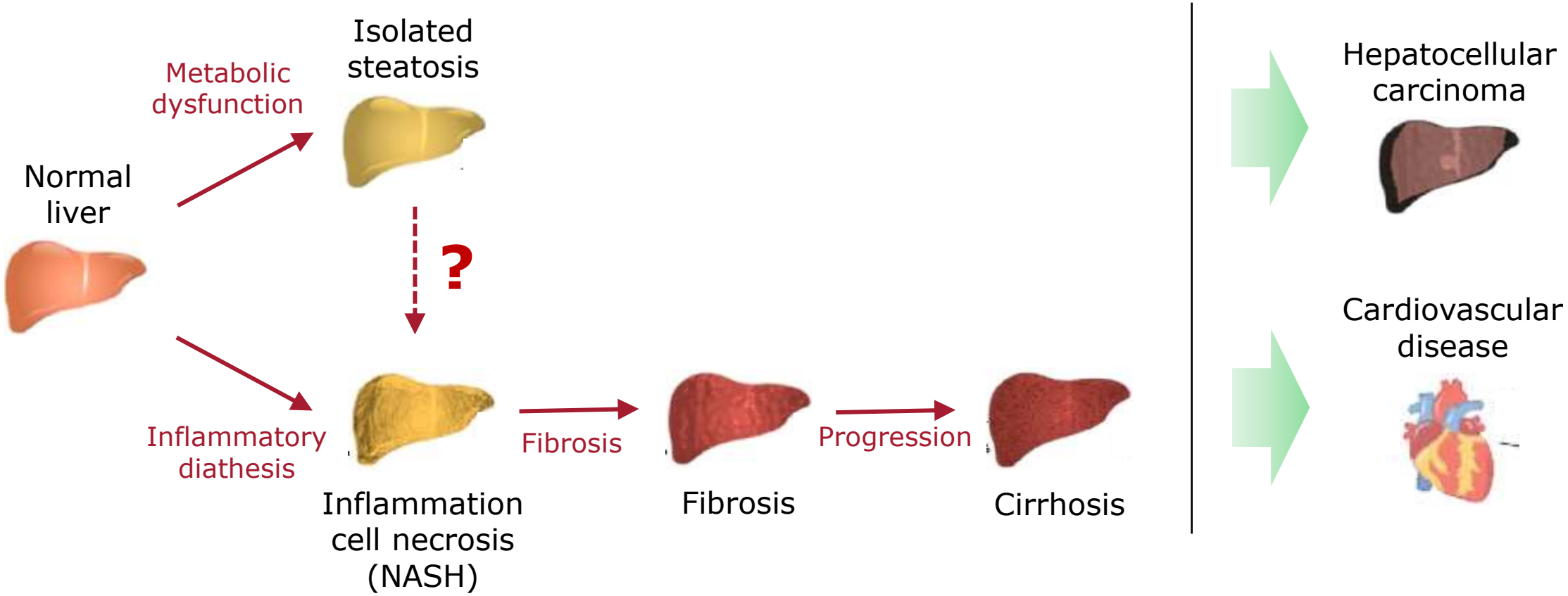
Prevalence of NAFLD and NASH



Worldwide prevalence of NAFLD is 25%

Worldwide prevalence of NAFLD among people with T2DM is 55.5%

NAFLD and its complications

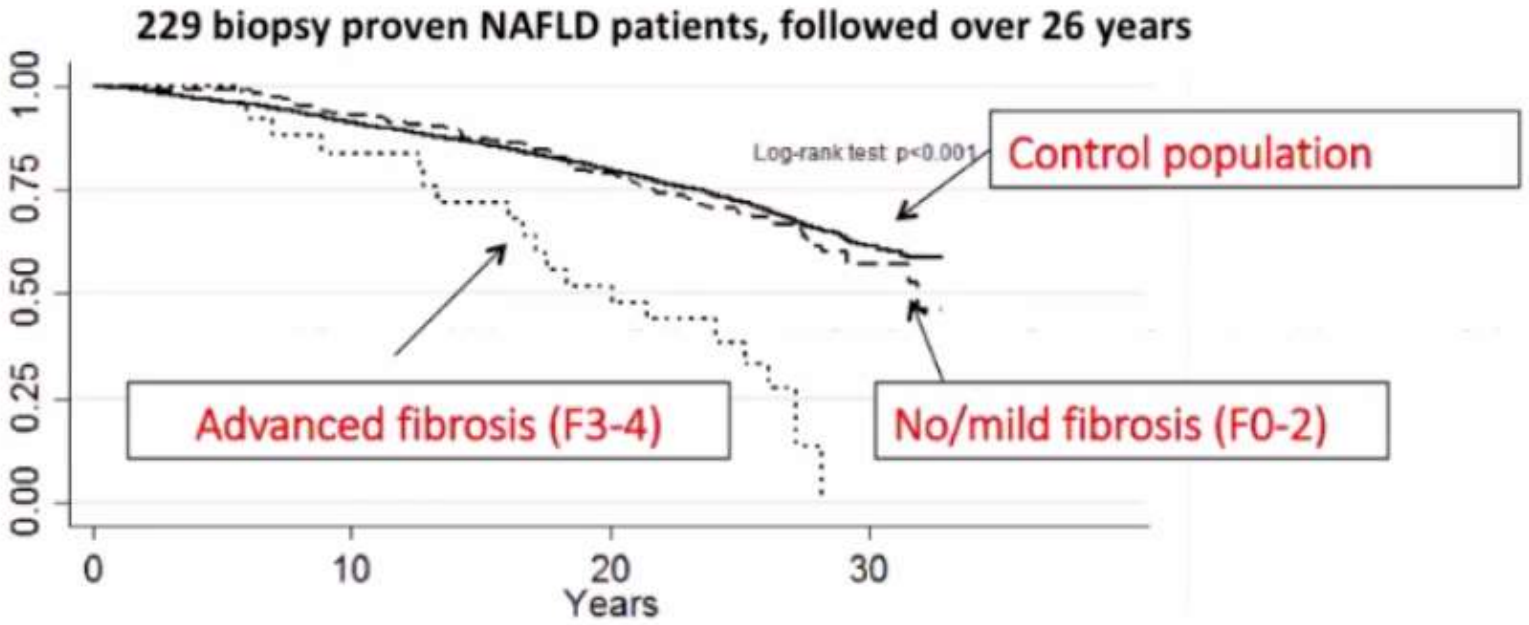


NAFLD histological scoring system

Two separate scores:

	Range
• **NAFLD activity score (NAS)**	**Range**
Steatosis	0-3
Lobular inflammation	0-3
Hepatocyte ballooning (cell injury)	0-2
Total score = sum	**0-8**
• **Fibrosis staging**	**F0-F4**

Advanced fibrosis is associated with all-cause and CV mortality

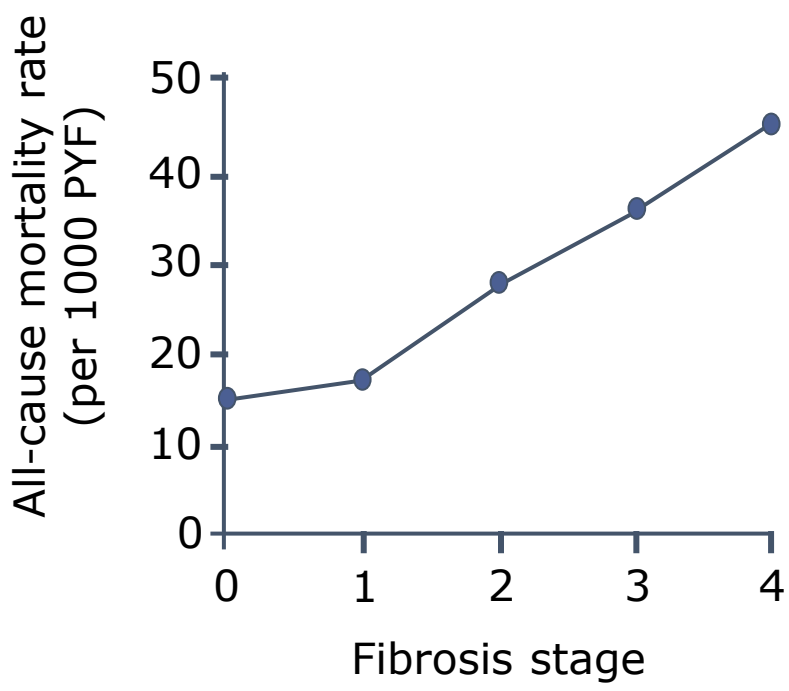


	Hazard ratios : fibrosis subgroup v control	
	No/mild fibrosis	Adv fibrosis
All-cause mortality	1.13 (0.79-1.60)	**3.28 (2.27-4.76)**
CV mortality	1.19 (0.65-2.20)	**4.36 (2.29-8.29)**

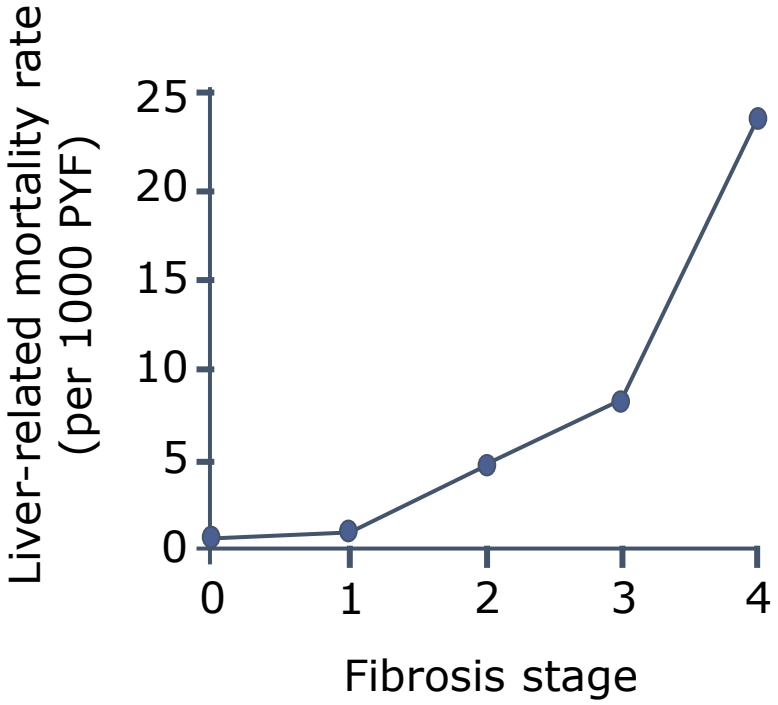
Eckhardt *et al.*, *Hepatology* 2015

Severity of liver fibrosis stage predicts mortality

All-cause Mortality



Liver-related Mortality



Weight loss is associated with remission of steatohepatitis

- Subjects: **293 adults** with NAFLD

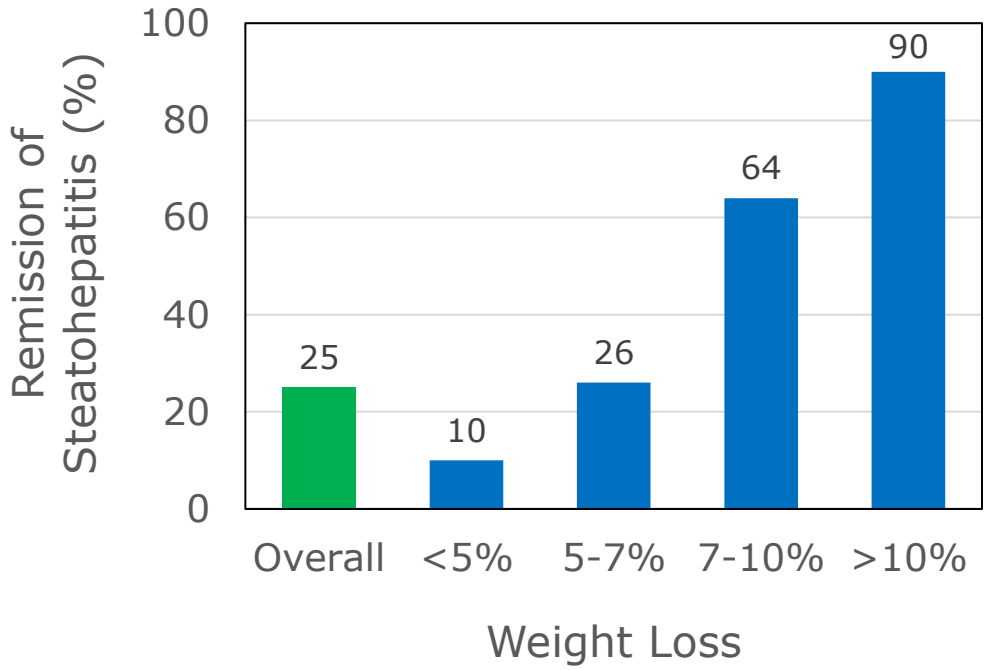
  Average NAS 4.8

  61% F0, 8% F1, 20% F2, 11% F3 (no F4)

- Intervention: 52 week treatment
  750 kcal/day deficit diet
  200 min/week exercise

- Average weight loss **3.8%**
  - **30% with weight loss ≥5%**

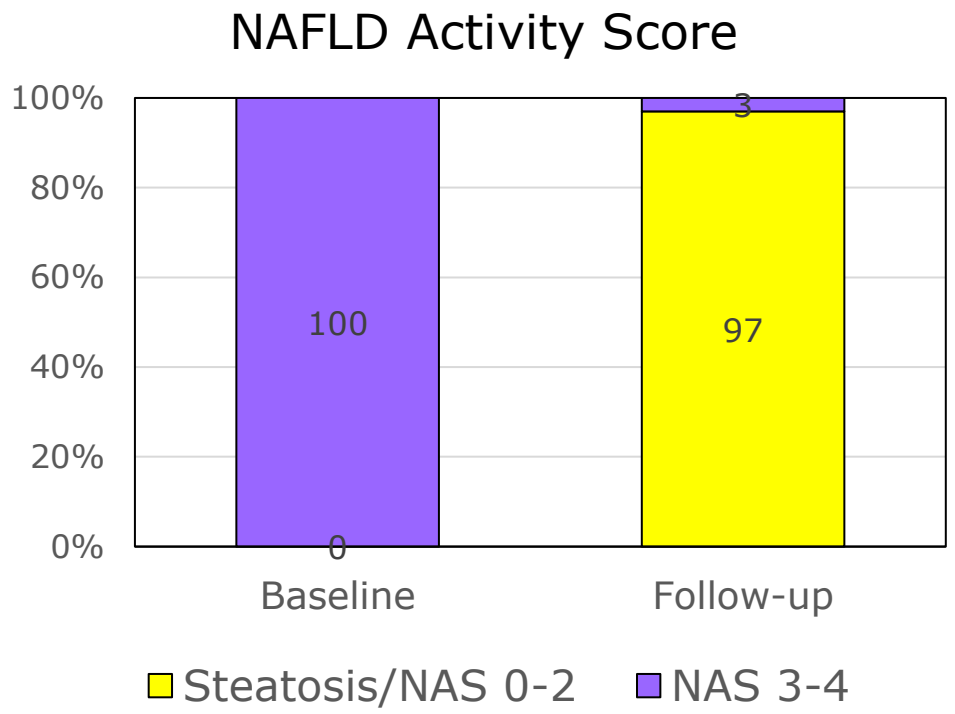
- Average change in NAS Score **-1.58**



Vilar-Gomez E *et al.*, *Hepatology* 2015

Bariatric surgery improves high activity NASH

(N=30)



Predictors of **Improvement** of High Activity NASH:

Shorter diabetes duration
Greater weight loss

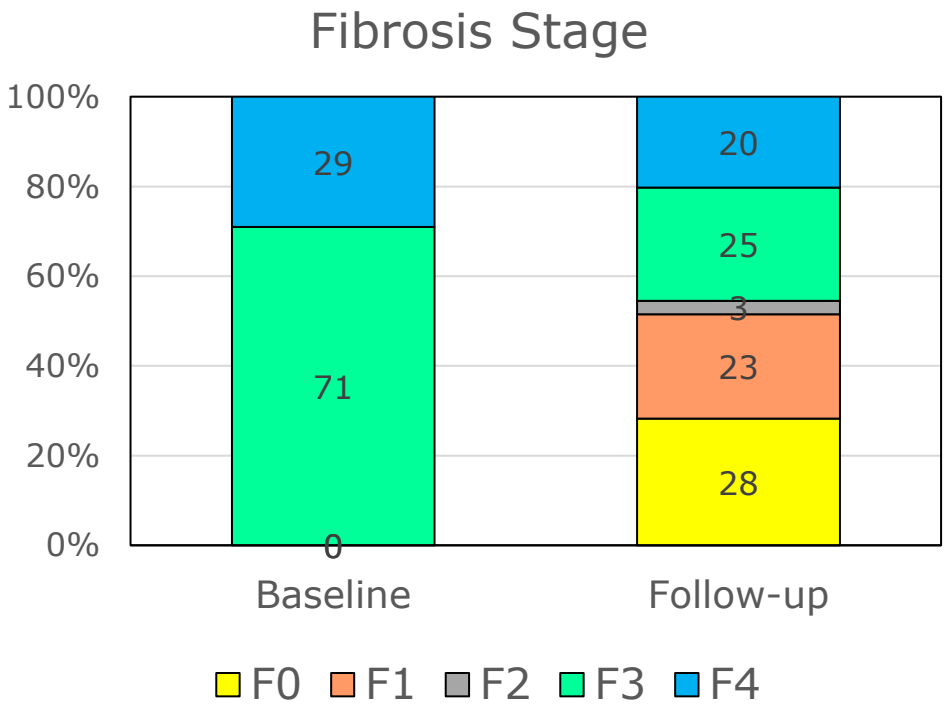
Absence of severe fibrosis predicted a normal follow-up biopsy (seen in 29%)

Pais R et al., Hepatology 2019; 45(Suppl 1):45

MASSACHUSETTS GENERAL HOSPITAL

Bariatric surgery improves severe fibrosis

(N=35)



Predictors of **Improvement** in Severe Fibrosis:

Younger
Improved T2D
Longer time until follow-up biopsy
Underwent **gastric bypass**

Pais R et al., Hepatology 2019; 45(Suppl 1):45

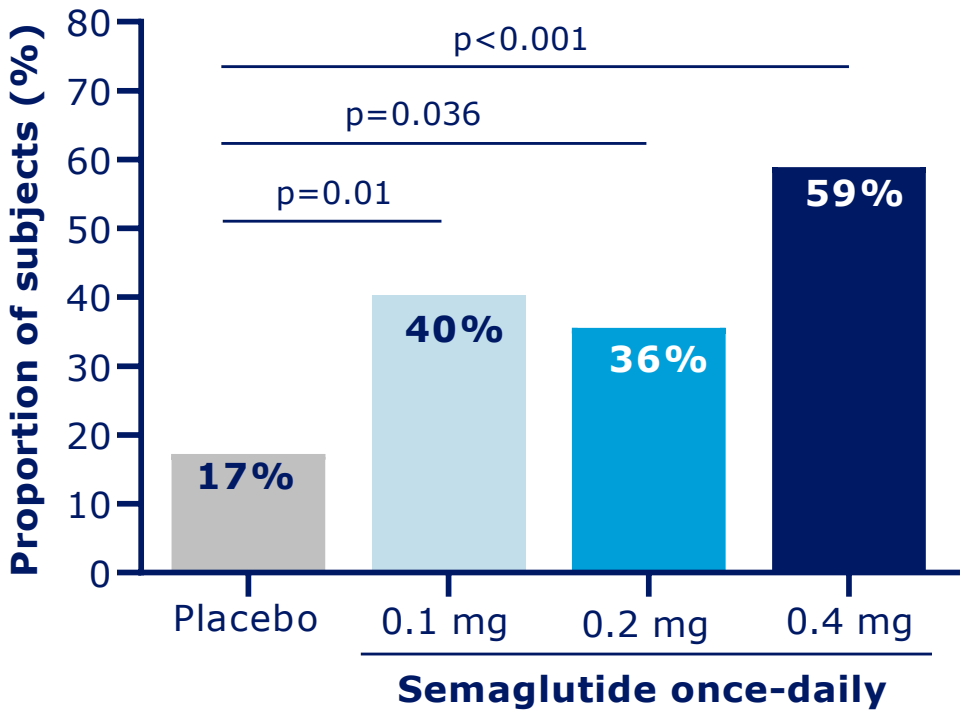
MASSACHUSETTS GENERAL HOSPITAL

Effect of bariatric surgery on NAFLD and NASH

- Immediate improvement in steatosis
- Effects on inflammation, cellular necrosis, and fibrosis less clear
  - Weight loss and other metabolic improvements after surgery provide hope of a benefit
  - No large or well-controlled studies; first well-controlled studies only recently started
- Effect of surgery to prevent progression to cirrhosis or hepatocellular carcinoma is currently unclear
- Mechanisms of benefit – weight loss alone vs. weight loss-independent metabolic effects – are not yet known

Semaglutide is effective against NASH in a phase 2 trial

- 320 participants with **stage 2 or 3 fibrosis** (not cirrhosis)
- 72-week treatment with semaglutide or placebo
- **Primary outcome 1: NASH resolution** without worsening of fibrosis
- **Primary outcome 2: Improvement in fibrosis** without worsening of NASH

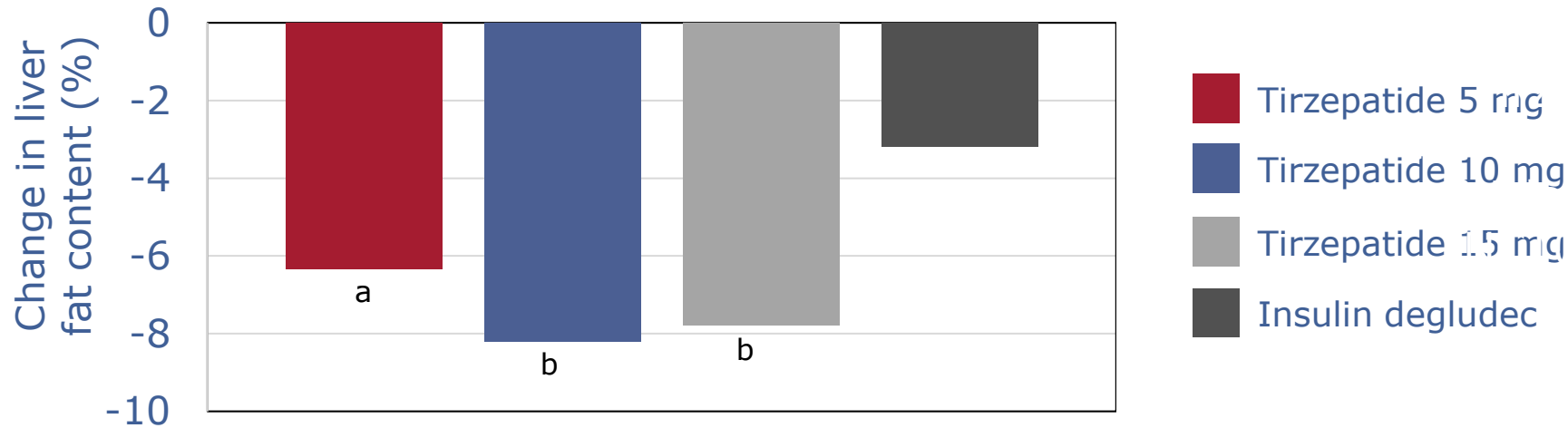


Newsome PN *et al*., *NEJM* 2020

Tirzepatide, a GLP-1/GIP dual agonist, reduces liver fat

SURPASS-3: Tirzepatide vs. insulin degludec in people with T2D and BMI≥25

Substudy in subjects with fatty liver index of ≥60
N=296
52 week treatment

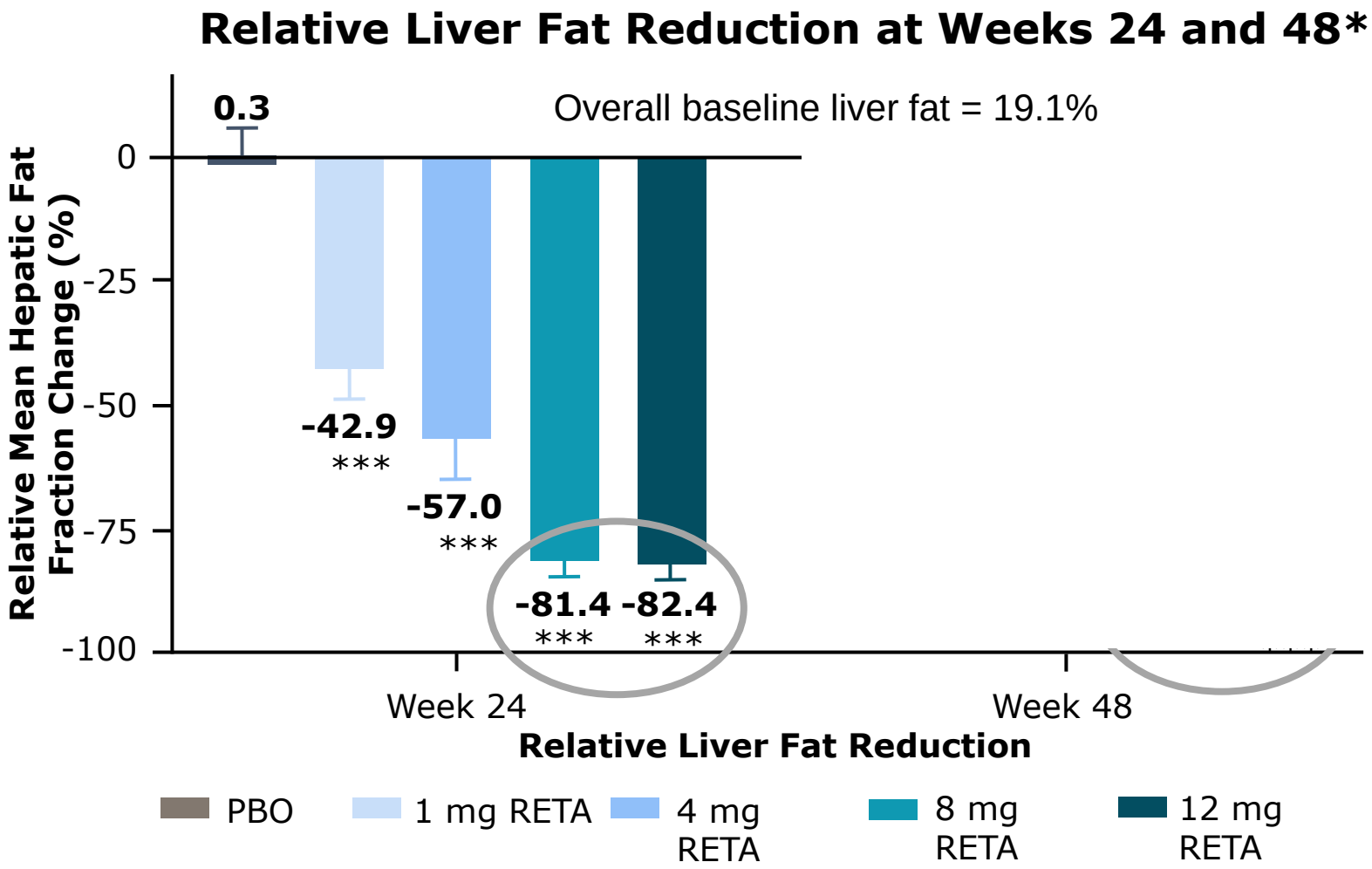


[a] *P* = .0056 vs insulin degludec; [b] *P* < .0001 vs insulin degludec

GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; T2D, type 2 diabetes; BMI, body mass index

Gastaldelli A, et al. *Lancet Diabetes Endocrinol* 2022

Retatrutide has a profound liver fat-reducing effect



- The relative change in liver fat was greater for all RETA doses than for PBO
- Mean relative liver fat reduction was >80% with RETA 8 mg and 12 mg
- Liver fat reduction occurred primarily in first 24 weeks of treatment

Sanyal A *et al.*, ADA Annual Meeting, San Diego, CA, June 2023

LMKaplan0@gmail.com

Beyond Glycemic Control: Bariatric Surgery and Metabolic Disease

Lee M. Kaplan, MD, PhD

Obesity Medicine Section and Dartmouth Obesity Care Center
Geisel School of Medicine at Dartmouth

LMKaplan0@gmail.com

31 August 2023

2023 IFSO World Congress