MAFLD: Endocrinologist Opinion injectable antihyperglycemic

By

Megahed Abouelmagd

Professor of diabetes and endocrinology

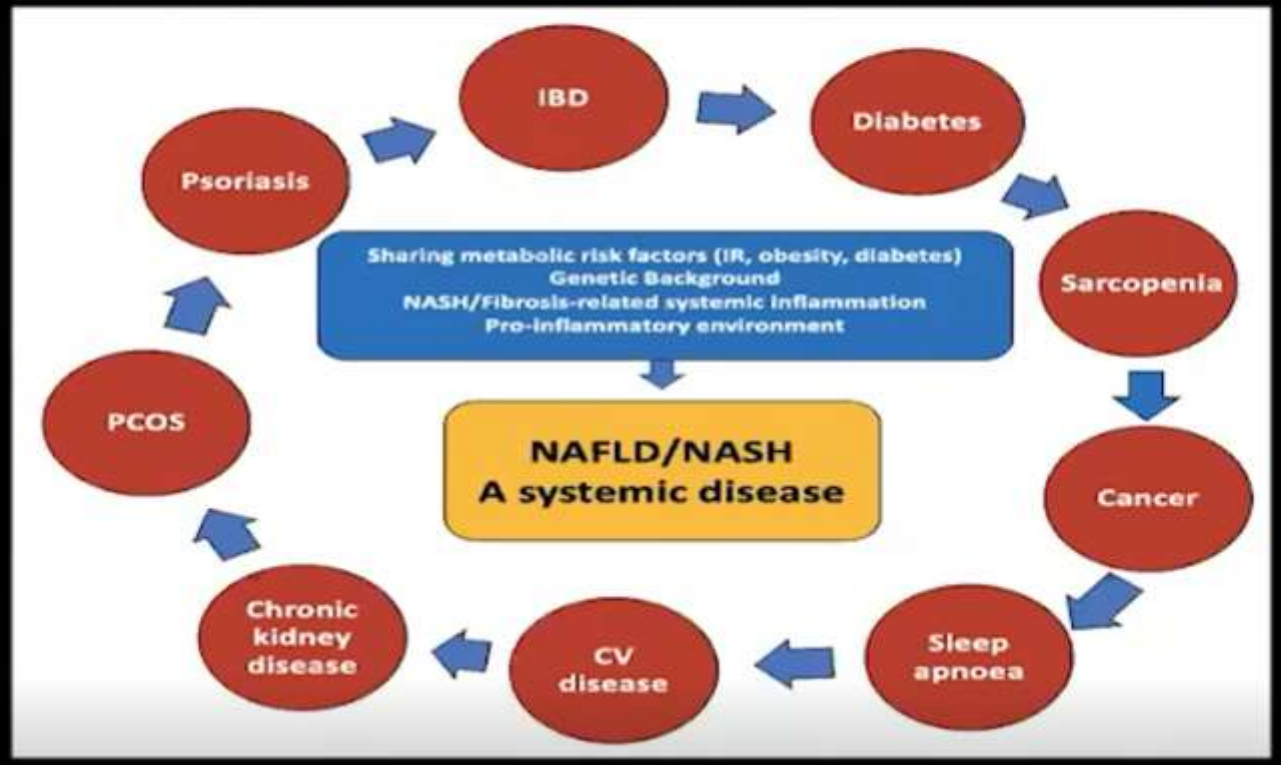
Mansoura

Introduction

- → NAFLD is currently one of the main causes of chronic liver disease in western countries, with a 25% prevalence reported in the general population worldwide.
- → NAFLD predicts the development of T2D and vice versa, and each condition may serve as a progression factor for the other

NAFLD or MAFLD?

- NAFLD is also regarded as a "metabolic disease" since it is closely associated with metabolic disorders including obesity, dyslipidem and diabetes mellitus, of which the common etiology is insulin resistance and higher risk of cardiovascular events.

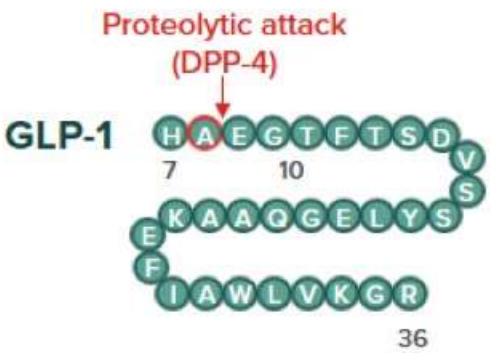


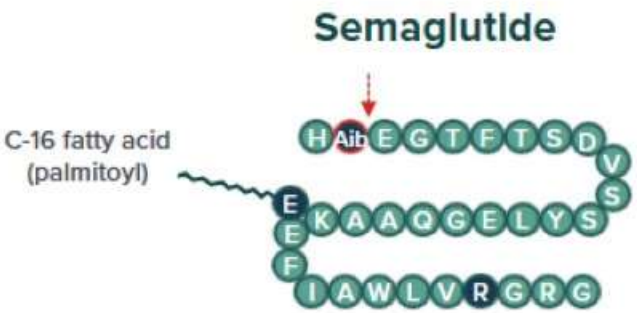
Role of Antidiabetic drugs in NAFLD

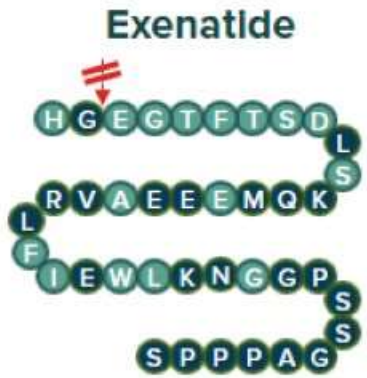
Injectable therapy

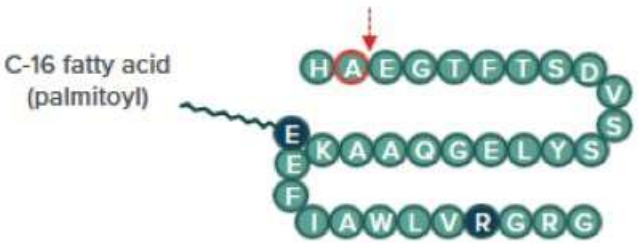
GLP-1 receptor agonists

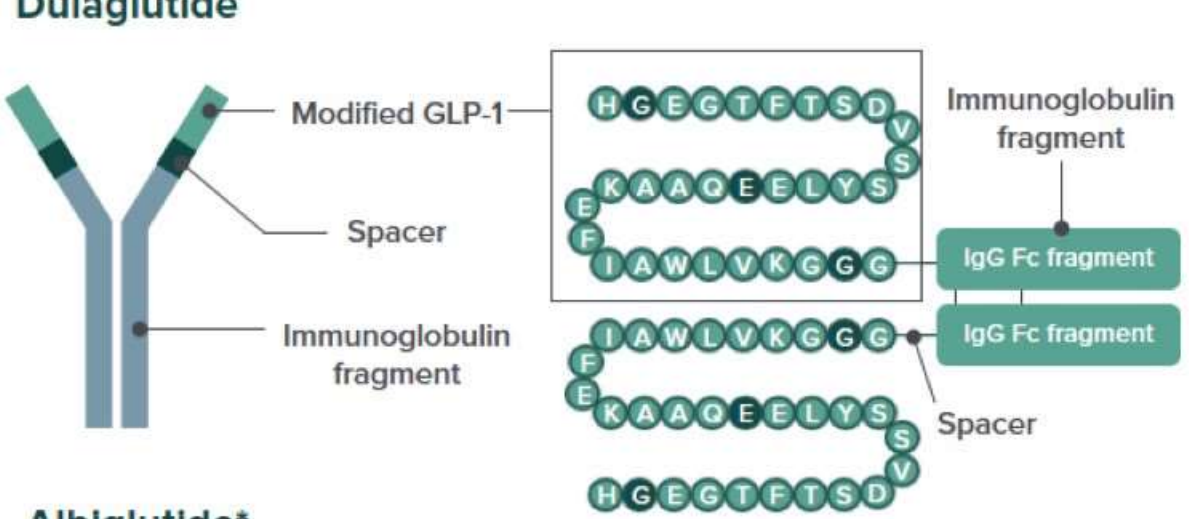
Contemporary Management of Diabetes
Incretin Agonists: GLP-1 Agonism

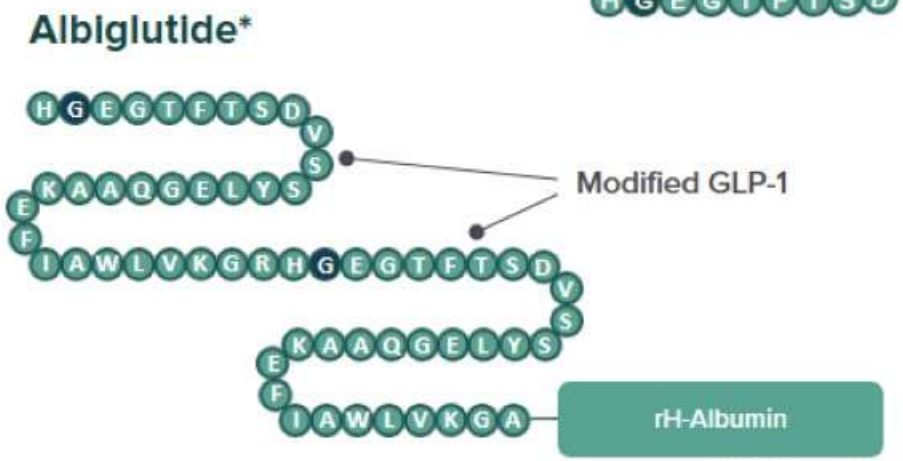








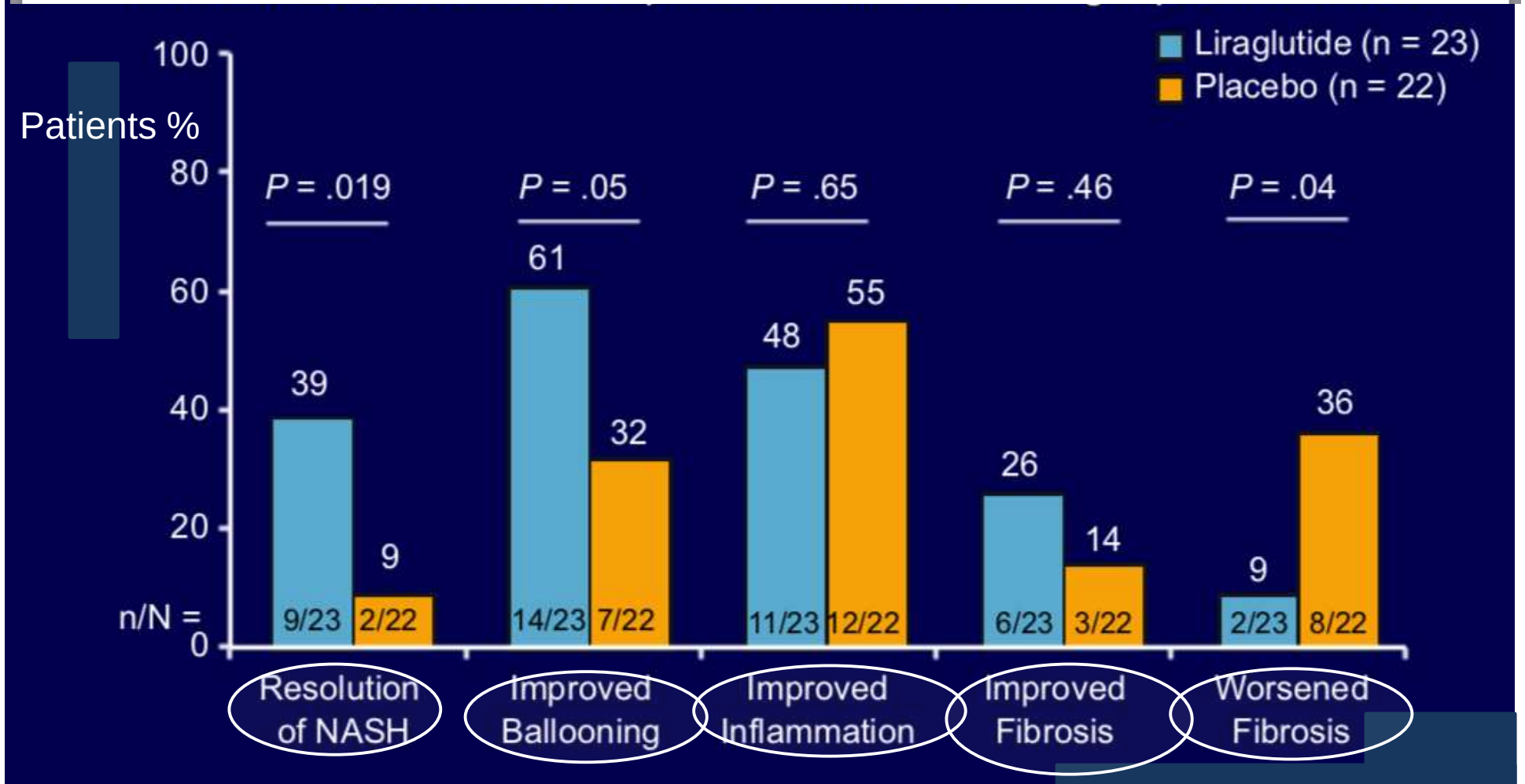




*Withdrawn in 2018 for economic reasons.
DDP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1.
Nauck MA, Meier JJ. Eur J Endocrinol. 2019;181:R211-R234.

LEAN Study: Liraglutide vs Placebo for NASH

- A 48-week phase 2 study of 52 participants with biopsy-proven NASH
- **Interventions**: liraglutide 1.8 mg *versus* placebo
- **Primary outcome**: Resolution of definite NASH with no worsening of fibrosis

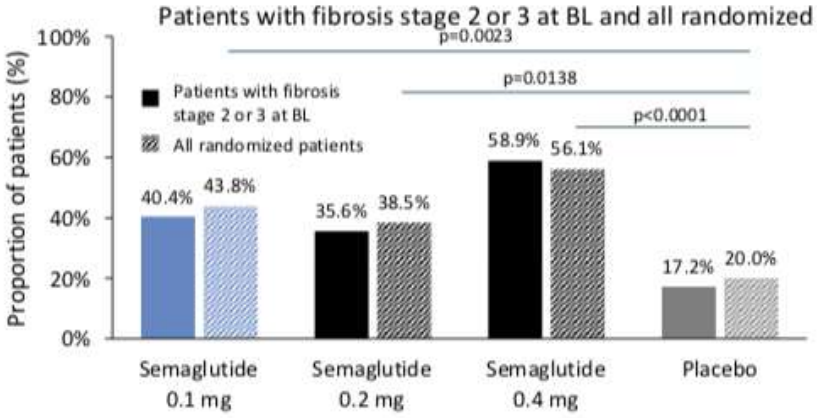


Armstrong MJ, et al. Lancet. 2016;387:679-690.

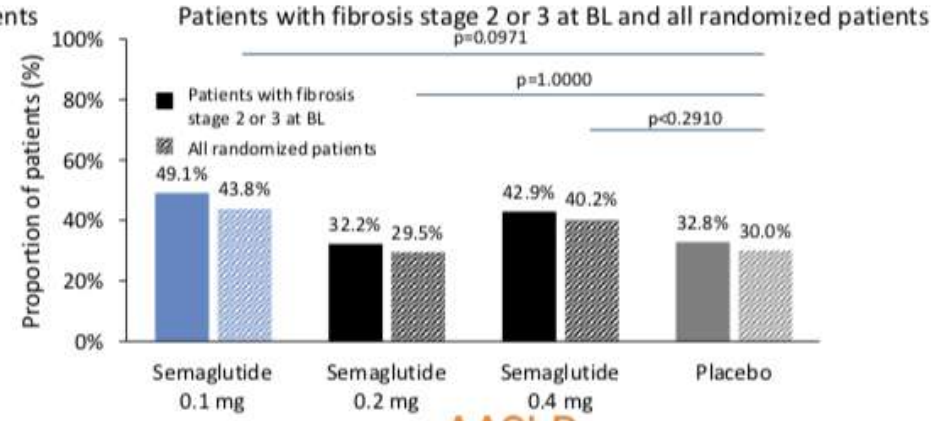
Semaglutide for NASH

- A 72-week, Phase 2 study of 320 participants with NASH, fibrosis stage 1, 2, or 3
- **Interventions**: Placebo vs semaglutide 0.1 , 0.2 or 0.4 mg subcutaneously daily
- **Primary outcome**: Resolution of NASH and no worsening in liver fibrosis

Resolution of steatohepatitis and no worsening in liver fibrosis



Improvement in liver fibrosis and no worsening in steatohepatitis



AASLD The Liver Meeting®

249

Treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo.

The trial did not show a significant between-group difference in the percentage of patients with an improvement in fibrosis stage.

Tirzepatide

Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes

Mark L. Hartman,[1] Arun J. Sanyal,[2] Rohit Loomba,[3,4] Jonathan M. Wilson,[1] Amir Nikooienejad,[1] Ross Bray,[1] Chrisanthi A. Karanikas,[1] Kevin L. Duffin,[1] Deborah A. Robins,[1] and Axel Haupt[1]

Diabetes Care 2020;43:1352–1355 | https://doi.org/10.2337/dc19-1892

Dual Incretin Agonism
Rationale For Synergism Between GIP And GLP-1

GIP and GLP-1 are physiological incretin hormones[a], ie, gut-derived peptides that stimulate insulin secretion

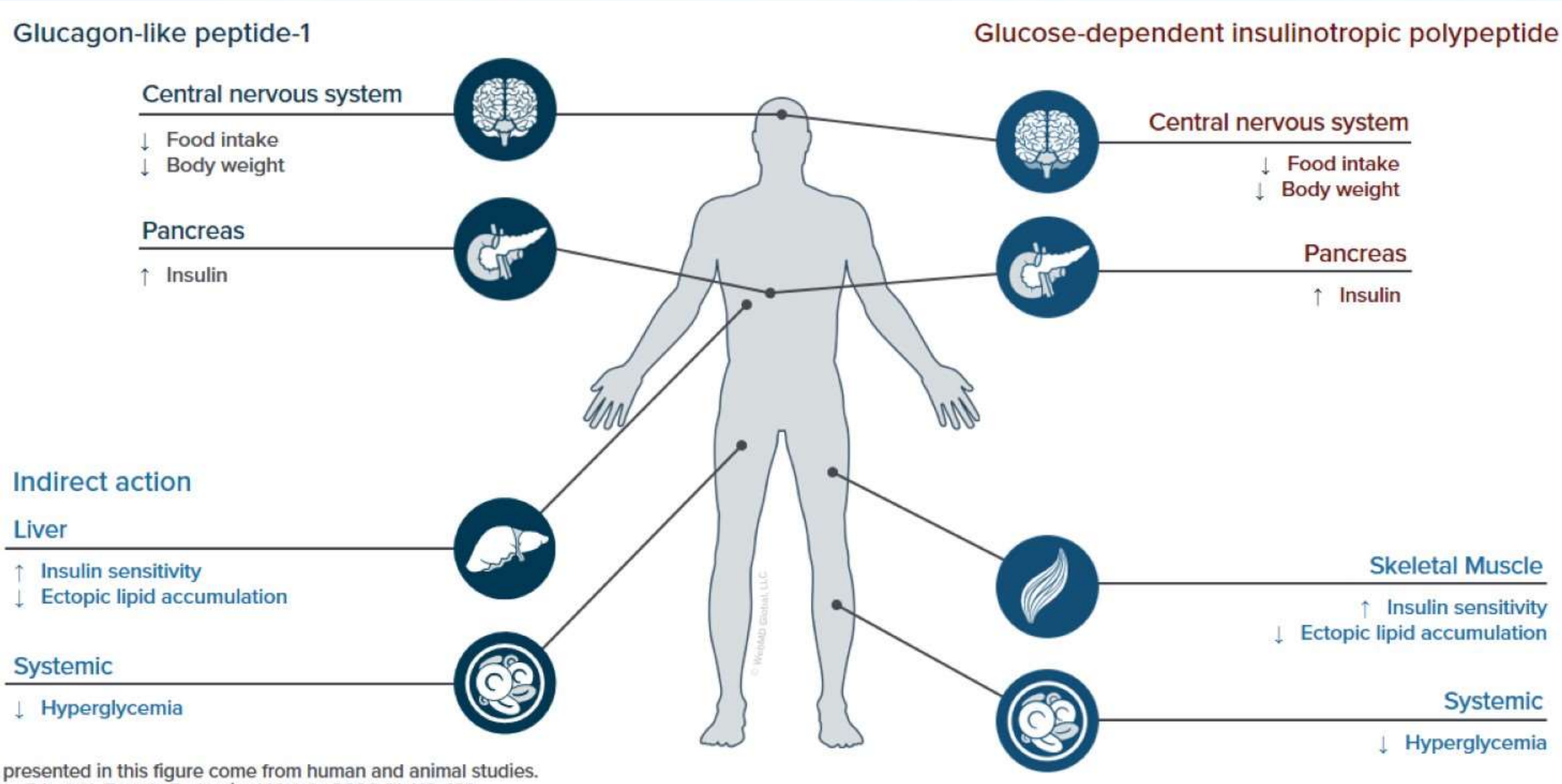
GIP and GLP-1 have additive effects[a] on insulin secretion

GLP-1 (greatly) and GIP (marginally)[a] are elevated after gastric bypass surgery (leading to significant weight loss and normoglycemia)

Trials results with a GIP/GLP-1 receptor co-agonist[b-f] reported significant reductions in HbA1c and body weight compared to GLP-1 receptor agonist alone

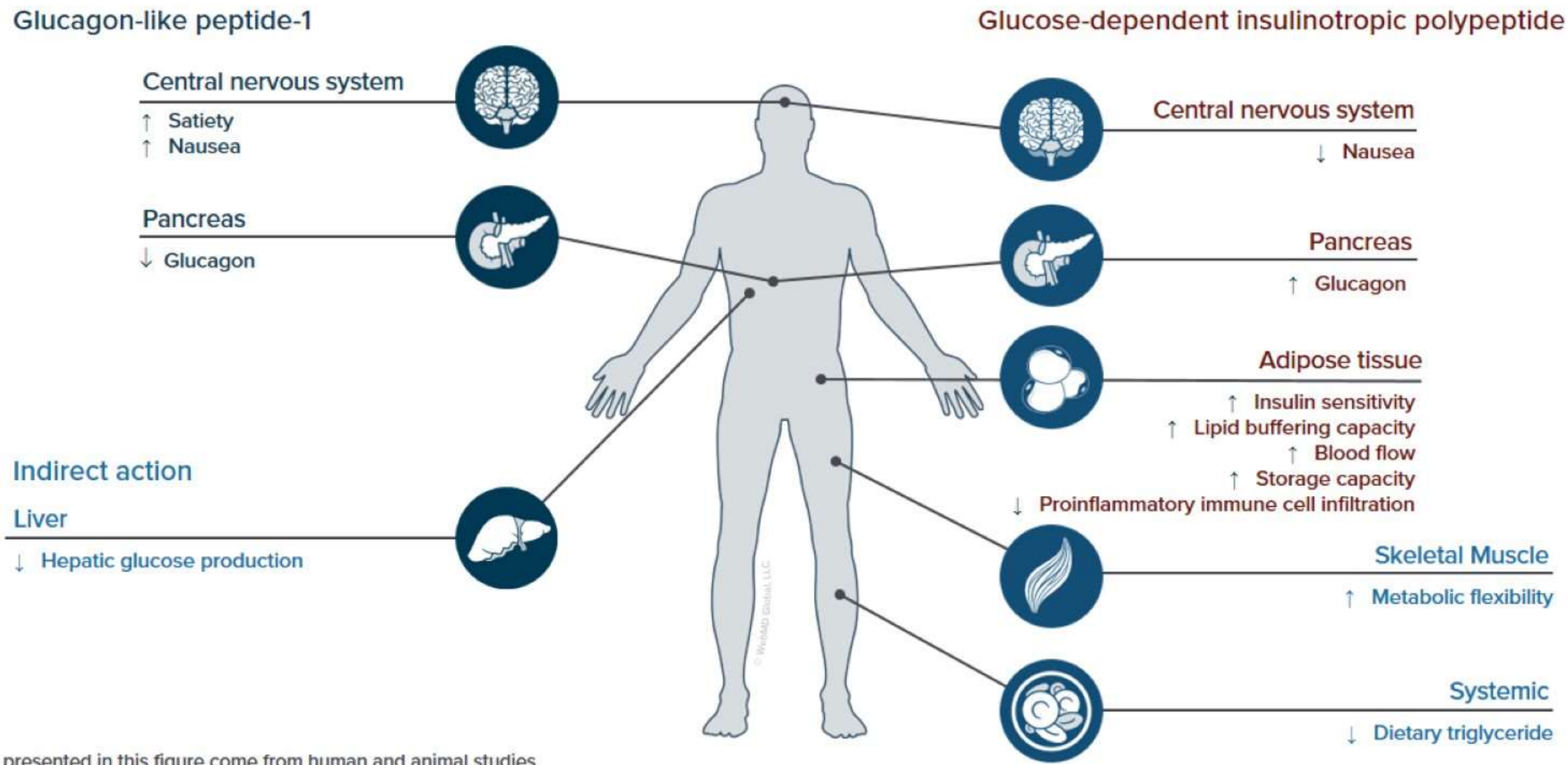
GIP, glucose-dependent insulinotropic polypeptide; GIPR, GIP receptor; GLP-1R, GLP-1 receptor.
a. Nauck MA, et al. Diabetes Obes Metab. 2021;23 Suppl 3:5-29; b. Rosenstock J, et al. Lancet. 2021;398:143-155; c. Frías JP, et al; SURPASS-2 Investigators. N Engl J Med. 2021;385:503-515; d. Ludvik B, et al. Lancet. 2021;398:583-598; e. Dahl D, et al. Presented at: 81st Scientific Sessions of the American Diabetes Association [virtual]; June 25-29, 2021. Poster 80-LB; f. Del Prato S, et al. Presented at: virtual EASD Annual Meeting 2021.

Similar Potential Pleiotropic Effects of GIP and GLP-1 Suggested by Preclinical and Clinical Data

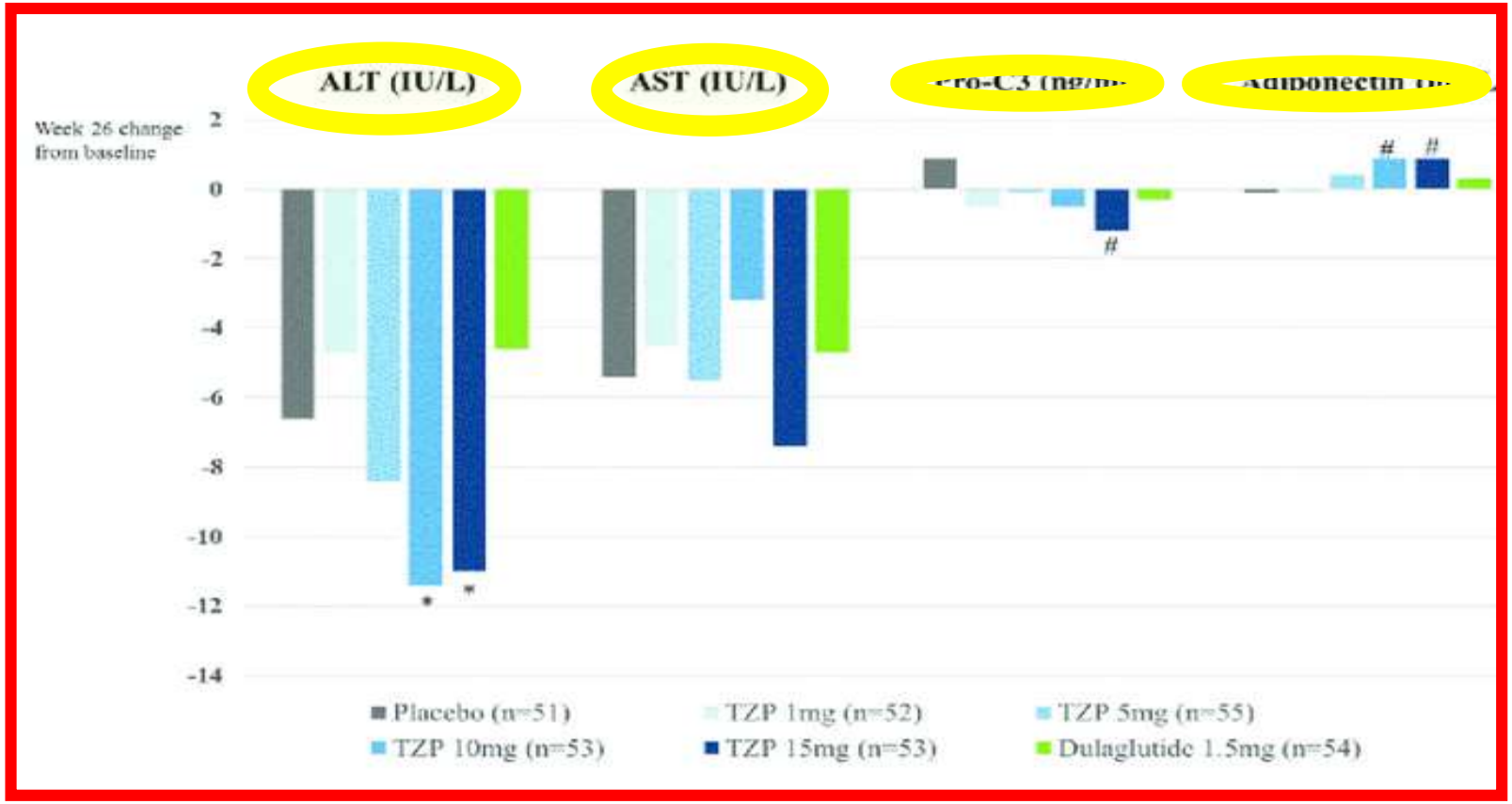


Data presented in this figure come from human and animal studies.
Samms RJ, et al. Trends Endocrinol Metab. 2020;31:410-421.

Different Potential Pleiotropic Effects of GIP and GLP-1 Suggested by Preclinical and Clinical Data



Data presented in this figure come from human and animal studies.
Samms RJ, et al. Trends Endocrinol Metab. 2020;31:410-421.



Tirzepatide significantly decreased NASH-related biomarkers and increased adiponectin in patients with T2DM.

Randomized Controlled Trial > Lancet Diabetes Endocrinol. 2022 Jun;10(6):393-406.
doi: 10.1016/S2213-8587(22)00070-5. Epub 2022 Apr 22.

Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

Amalia Gastaldelli [1], Kenneth Cusi [2], Laura Fernández Landó [3], Ross Bray [3], Bram Brouwers [3], Ángel Rodríguez [4]

Affiliations + expand

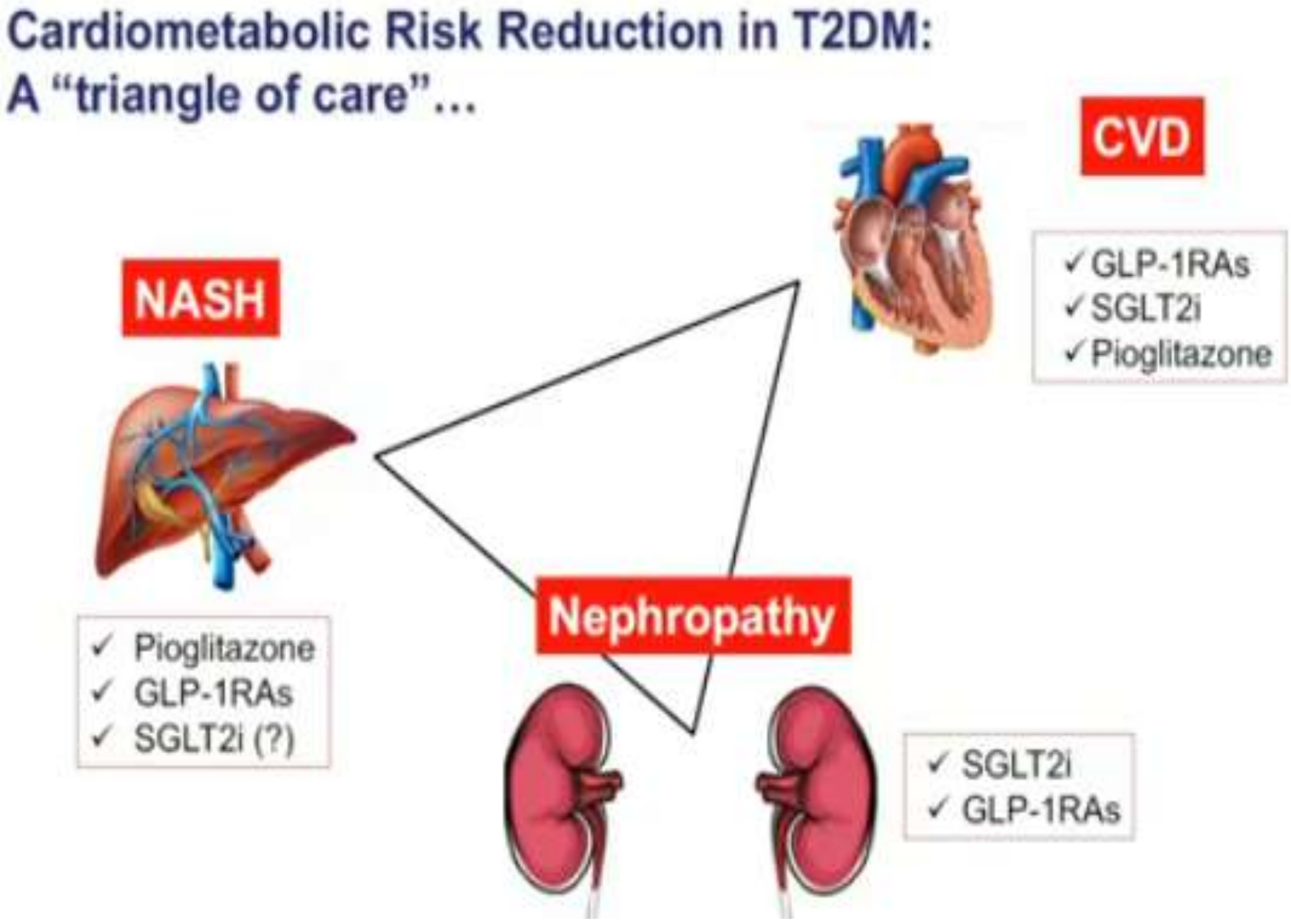
PMID: 35468325 DOI: 10.1016/S2213-8587(22)00070-5

- Tirzepatide 10 mg and 15 mg were found to **reduce liver fat content** by **more than half** (by 8.09%, from a baseline of 15.71%) after **1 year of treatment**. The active comparator, insulin degludec, reduced fat levels by 3.38%.
- These results position tirzepatide as a promising future treatment for NAFLD.

Recent randomized controlled trials of biopsy-proven NAFLD including anti-diabetic agents in recruitment

Name	Design	Estimated enrollment	Start date	Completion date
DEAN	Dapagliflozin 10 mg/d versus placebo	100 patients	March 20, 2019	June, 2022
SYNERGY-NASH	**Tirzepatide** 5, 10, 15 mg/week versus placebo	196 patients	November 19, 2019	**June, 2022**
REALIST	**Dulaglutide** 1.5 mg/week + diet versus dietary monitoring only	93 patients	September 1, 2019	March 30, 2024
COMBAT_T2_NASH	Empagliflozin 10 mg/d + semaglutide 1 mg/week versus empagliflozin versus placebo	192 patients	March 26, 2021	December 2023
AIM 2	Pioglitazone 15 mg/d versus placebo	138 patients	December 15, 2020	February 29, 2024

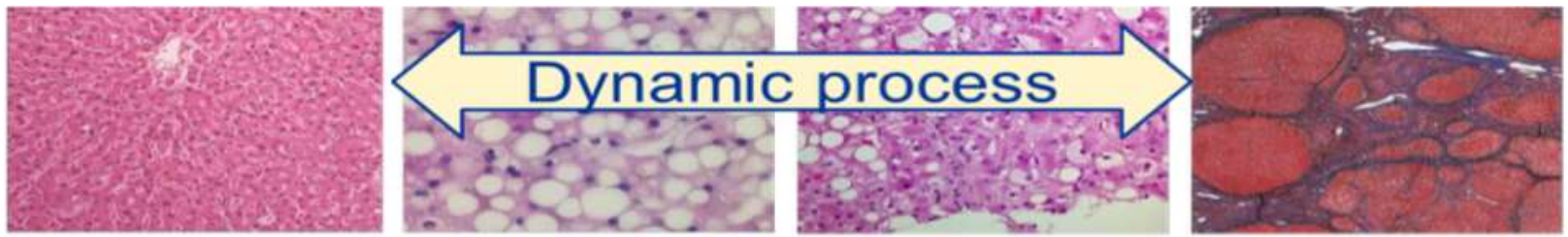
Conclusion

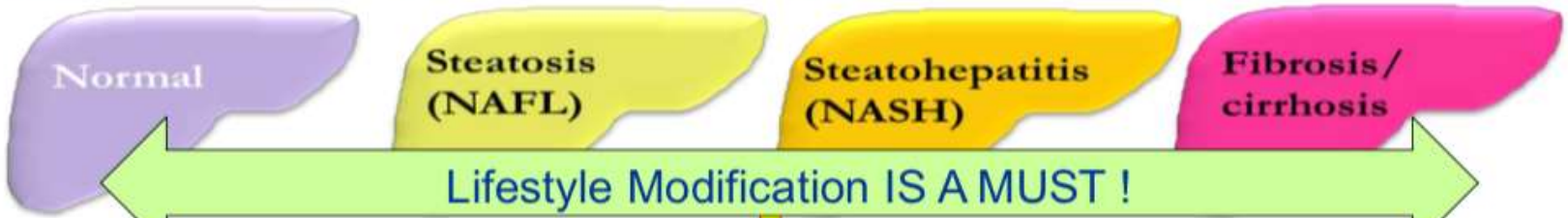

Cardiometabolic Risk Reduction in T2DM:
A "triangle of care"…
CVD
✓ GLP-1RAs
✓ SGLT2i
✓ Pioglitazone
NASH
✓ Pioglitazone
✓ GLP-1RAs
✓ SGLT2i (?)
Nephropathy
✓ SGLT2i
✓ GLP-1RAs

- A serological marker for DM-related liver diseases should be investigated. A recent study has shown, for example, that the circulating level of **osteopontin** (OPN), a soluble pluripotent glycophosphoprotein and a **proinflammatory cytokine**, may be useful in diagnosing NAFLD in patients with DM.

- We need to change the conception that clinical studies on the management of DM have traditionally focused on the **micro-/macrovascular complications** of prolonged hyperglycemia instead of liver disease-related clinical outcomes.

Current Treatment of NAFLD





Lifestyle Modification IS A MUST !

Targeted Pharmacotherapy for FDA approved indications
Targeting co-morbidities of NAFLD/NASH
(metformin, vitamin E, pioglitazone, GLP-1 Ras, SGLT2 inhibitors, statins)

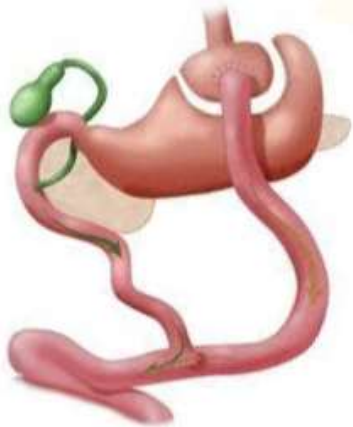
Medical treatment unsuccessful: Consider bariatric endoscopy or surgery or referral for clinical trials

Alternatives Anti-Obesity Approaches

FDA Approved Anti-Obesity Drug

Bariatric Endoscopy

Bariatric Surgery



AASLD The Liver Meeting®

Pharmacotherapy Targeting Weight Loss and Insulin Resistance (Off Label)

Mechanism of Action	Compound	Weight Loss	Trial in NAFLD/NASH	Outcome
GLP-1 RA	Exenatide [1]	+	Phase 2b	Improvement of hepatic steatosis by ultrasound
	Liraglutide	+ Approved for obesity	L Trial	Resolution of NASH without worsening fibrosis
	Semaglutide	+++ Approved for obesity and diabetes	Phase 2b	Resolution of ANSH without worsening fibrosis
SGLT2	Canagliflozen	++	Multiple studies	Improvement in liver triglyceride by 1H-MRS; improvement in steatosis biomarkers
	Empagliflozin	+	Multiple studies	Improvement in liver fat by MRI-PDFF Improvement in CAP and liver stiffness by TE

CAP= Capture attenuation parameter; TE = transient elastography

Shao. Diabetes/Metabolism Research Reviews. 2014;30:521. 2. Armstrong. Lancet. 2016;387:679-690. 3. Newsome. NEJM. 2021;384:1113. 4. Cusi. Diabetes Obes Metab. 2019;21:812.
5. Kuchay. Diabetes Care. 2018;41:1801. 6. Taheri. Advanc Ther. 2020;37:4697.

Treatment of Obesity is Foundation of Care

5% reduction in BMI → 25% relative reduction in liver fat by MRI PDFF.[1]

Systematic review of 23 studies: weight reduction of 4–10% consistently improves measures of liver fat or serum transaminase levels.[2]

Patel et al. Clin Gastroentrol Hepatol. 2015.[1]
Thoma et al. J Hepatol. 2012.[2]

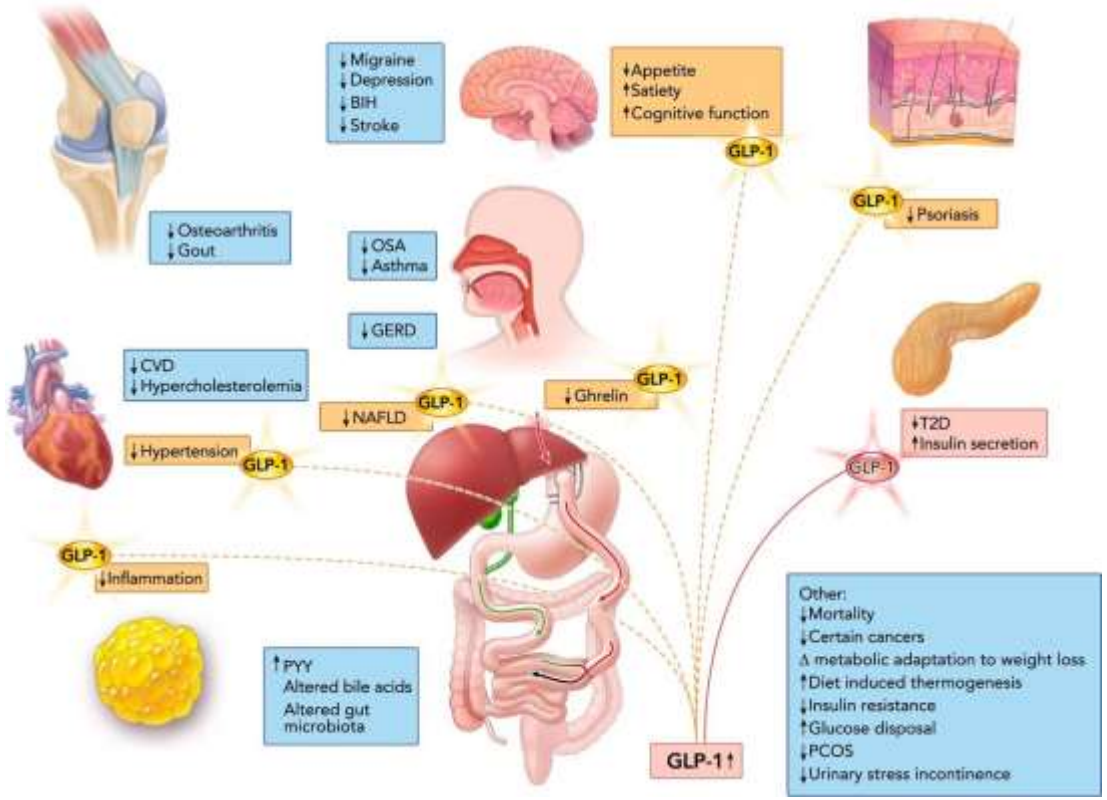
Bariatric Surgery Changes the Gut Neuro-Endocrine Milieu

Gut/pancreatic peptide hormone	Secretion after gastric bypass	Effect on body weight		Effect on glycemia
		Appetite	Energy expenditure	
GLP-1	↑↑↑	↓↓	↑*	↓ FPG, ↓↓PPG
Glucagon	↑	≈	↑	↑ FPG, ↑ PPG
GIP	↑	(↓/ ↑)†	≈	↓ FPG, ↓ PPG
PYY	↑↑	↓↓	≈	↓ FPG, ↓ PPG‡

*Potentially increased; †conflicting data; ‡hypothetically decreased FPG and PPG (no quantitative data available).

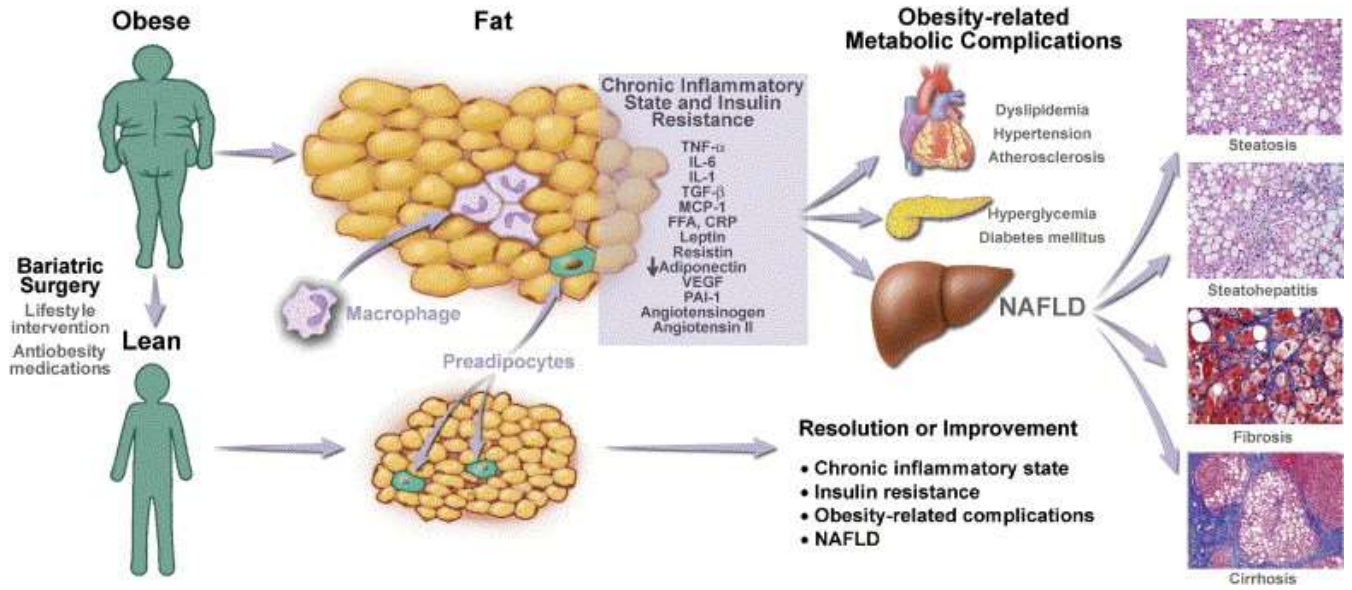
FPG, fasting plasma glucose; PPG, postprandial glucose; PYY, peptide YY.

Nauck MA, et al. Lancet Diabetes Endocrinol. 2021;9:525-544.

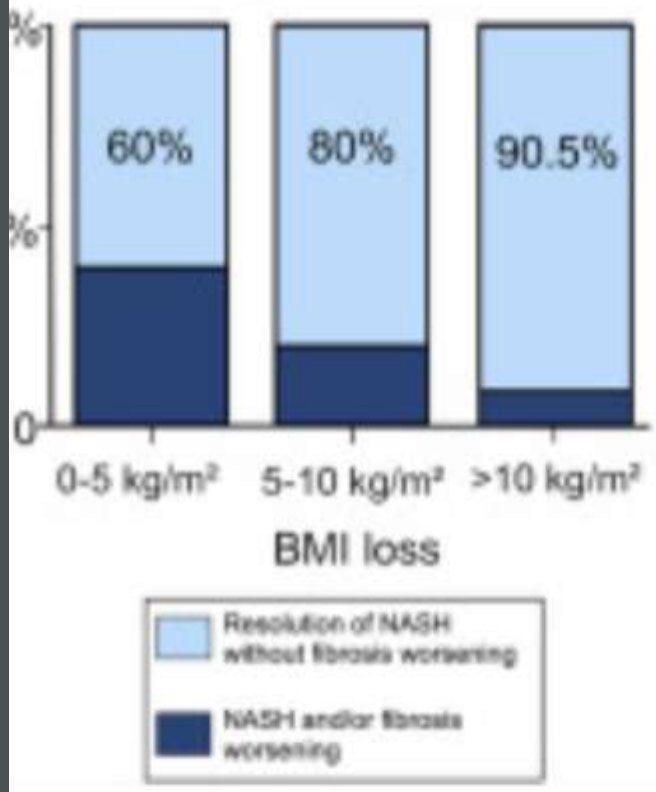


Schematic diagram illustrating the multisystem benefits of bariatric surgery (all boxes), including the benefits likely to be mediated by GLP-1 (red coded), those potentially mediated by GLP-1 (orange coded), and those unlikely to be mediated by GLP-1 (blue coded). CVD, cardiovascular diseases; OSA, obstructive sleep apnoea; GERD, gastroesophageal reflux disease; BIH, benign intracranial hypertension; PCOS, polycystic ovary syndrome.

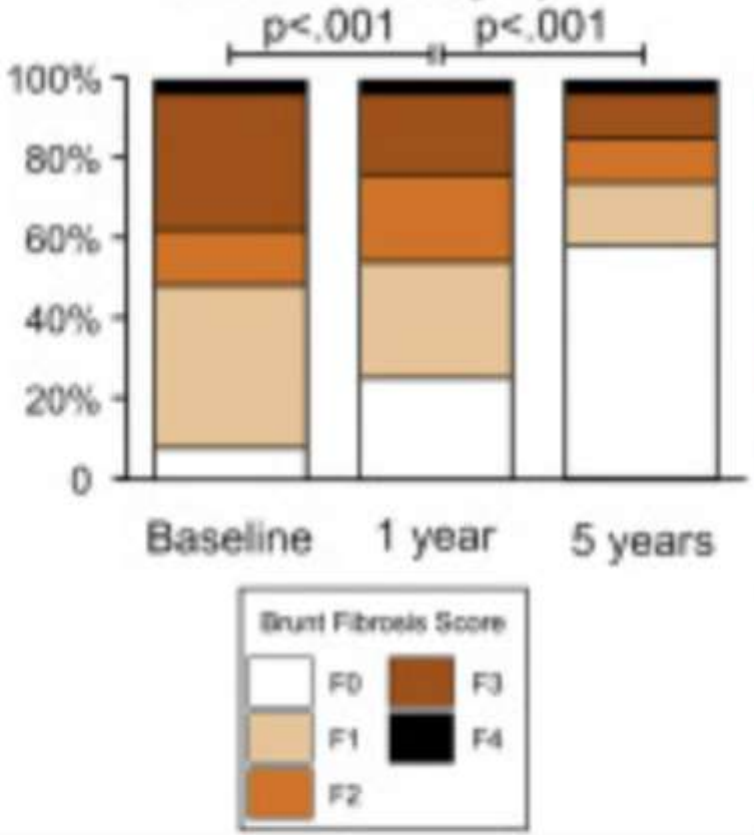
DOI: (10.1152/physiol.00027.2014)



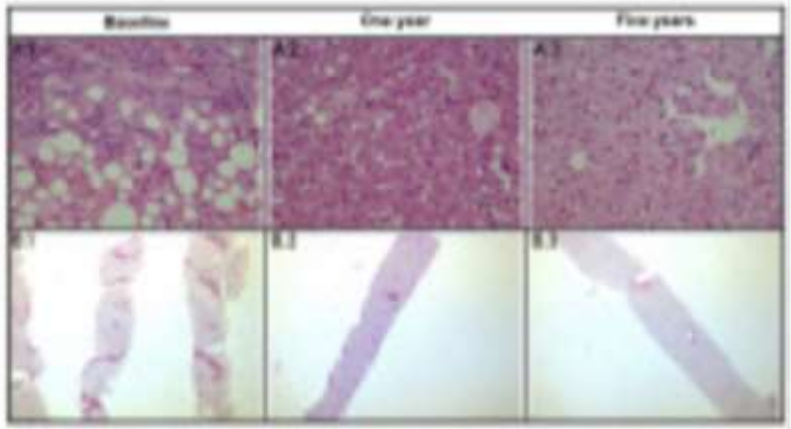
solution of NASH according to weight loss



Evolution of Fibrosis after Bariatric Surgery



Histological Evolution of NASH and Fibrosis after Bariatric Surgery



A: Upper panel H&E staining, (X400)

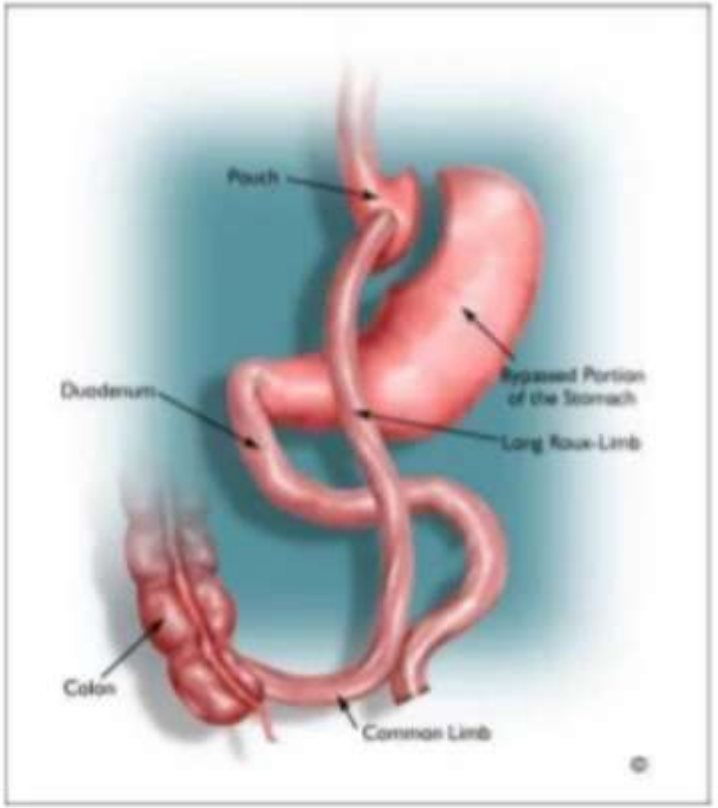
B: Lower panel Sirus Red staining, (X25)

Gastroenterology

Weight loss: surgical

Meta-analysis of bariatric surgery assessing 766 paired liver biopsies from 15 studies reported:

- improvement in steatosis in 91.6%
- improvement in steatohepatitis in 81.3%
- improvement in fibrosis in 65.5%
- complete NASH resolution in 69.5%
- improvements occurred primarily in patients showing the greatest improvement in components of metabolic syndrome and insulin resistance.



[Mummadi et al, Gastroent Hepatol 2008]

Insulin

- **2 Opposing mechanisms**:
  - On the one hand, cirrhosis can induce or exacerbate insulin resistance, which may increase a patient's insulin requirement.
  - On the other hand, cirrhotic patients may exhibit an exaggerated response to insulin due to impaired hepatic gluconeogenesis.
- These opposing mechanisms of actions, make it difficult to predict a patient's day-to-day exogenous insulin requirement.
- As such, expert opinions recommend the use of short-acting insulin analogs as well as frequent dose adjustment and close glucose monitoring to minimize the risk of hypoglycemia.

Insulin

Observational studies

suggest an association between insulin therapy and HCC development amongst patients with T2DM

Expert opinions advise to reserve insulin therapy in patients with CLD to those who are unable to receive or inadequately managed by other antihyperglycemic medications

So, NAFLD may be the upcoming concern in management of type 2 DM

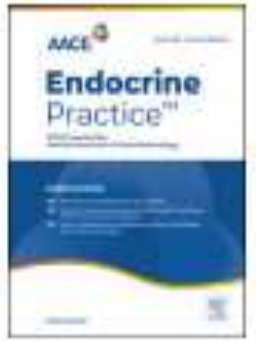
In conclusion

Endocrine Practice 28 (2022) 528–562

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org



Clinical Practice Guidelines

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)

Kenneth Cusi, MD, FACE, FACP, Co-Chair [1,*], Scott Isaacs, MD, FACE, FACP, Co-Chair [2], Diana Barb, MD, ECNU [3], Rita Basu, MD [4], Sonia Caprio, MD [5], W. Timothy Garvey, MD, MACE [6], Sangeeta Kashyap, MD [7], Jeffrey I. Mechanick, MD, ECNU, MACE, FACP, FACN [8], Marialena Mouzaki, MD, MSc [9], Karl Nadolsky, DO, FACE, DABOM [10], Mary E. Rinella, MD, AASLD Representative [11], Miriam B. Vos, MD, MSPH [12], Zobair Younossi, MD, AASLD Representative [13]

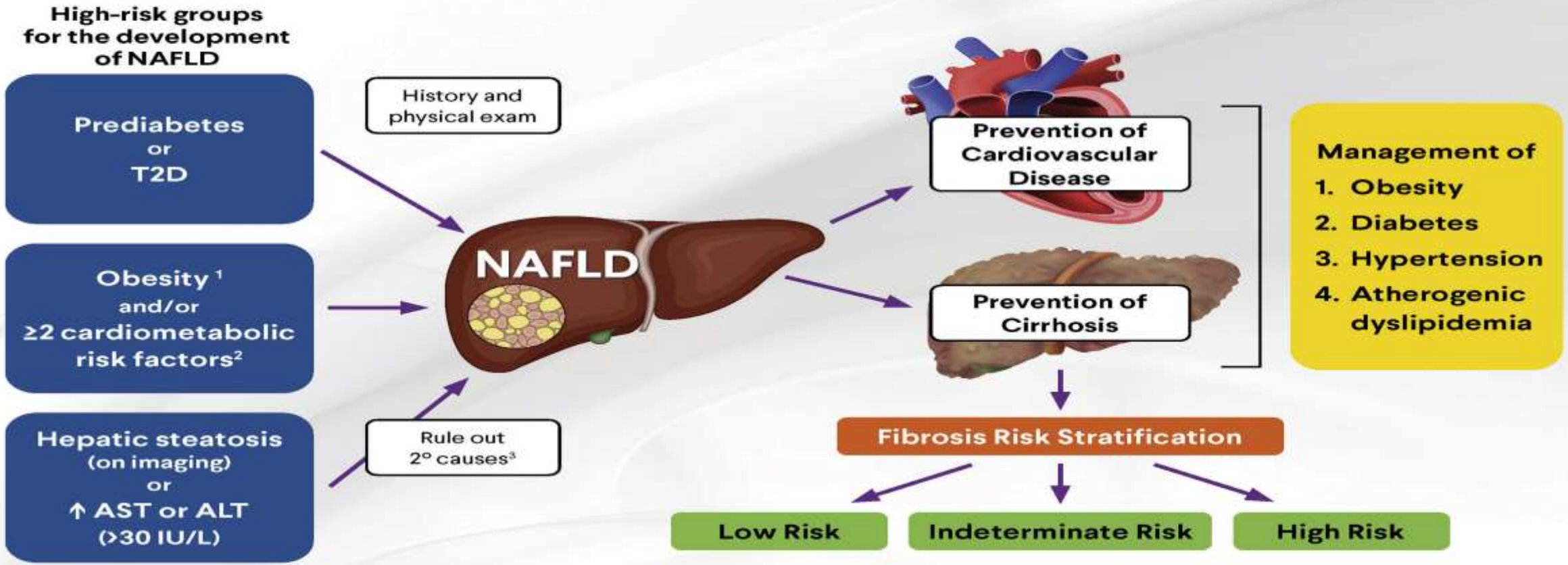
Management Algorithm for Persons with NAFLD

in Primary Care and Endocrinology Clinical Settings

Table of Contents

Algorithm Fig. 1

Management Algorithm for NAFLD – Overview



Abbreviations: ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T2D = Type 2 diabetes mellitus

1. Adiposity-based chronic disease (ABCD) is a diagnostic term proposed by AACE to better describe the disease of obesity in a complication-centric manner of abnormal adipose tissue mass, distribution, function and resulting morbidity that can be ameliorated with weight loss.
2. Cardiometabolic risk factors of the metabolic syndrome are waist circumference >40 inches men >35 inches women, triglycerides ≥150 mg/dL, HDL-C <40 mg/dL men, <50 mg/dL women, BP ≥130/≥85 mm Hg, fasting plasma glucose ≥100 mg/dL (NCEP ATP III)
3. Secondary causes of liver steatosis or elevated transaminases (AST or ALT) are excessive alcohol consumption (≥14 drinks/week for women or ≥21 drinks/week for men), hepatitis B, hepatitis C (genotype 3), Wilson's disease, alpha 1 antitrypsin deficiency, lipodystrophy, starvation, parenteral nutrition, abetalipoproteinemia, hemochromatosis, mass lesions, medications and other causes.

Algorithm Figure 1

AACE.

Thank you

Any questions?