
به نام خداوند جان و خرد

OBESITY &NAFLD

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OBESITY DEFINITION

- **WHO : “abnormal or excessive fat accumulation that may impair health”**

- **Obesity is a chronic disease requiring long-term management.**

WHO. Factsheet 311. 2014. http://www.who.int/

OBESITY

Weight categories for adults and youth

Category	Adults 18 years and older[1] (kg/m²)	Youth 2 to 18 years (CDC, AAP, IOM, ES, IOTF[2])
Underweight	BMI <18.5	BMI <5th percentile for age
Normal weight	BMI 18.5 to <25	BMI ≥5th to <85th percentile
Overweight	BMI 25 to <30	BMI ≥85th to <95th percentile
Obesity		
▪ Class I obesity	BMI ≥30 to <35	BMI ≥95th percentile to <120% of the 95th percentile or BMI ≥30 to <35 (whichever is lower)
▪ Class II obesity	BMI ≥35 to <40	BMI ≥120 to 140% of the 95th percentile or a BMI ≥35 to <40 (whichever is lower)*
▪ Class III obesity	BMI ≥40	BMI ≥140% of the 95th percentile or a BMI ≥40 (whichever is lower)

CDC: Centers for Disease Control and Prevention; AAP: American Academy of Pediatrics; IOM: Institute of Medicine; ES: Endocrine Society; IOTF: International Obesity Task Force; BMI: body mass index.

* 120% of the 95th percentile corresponds to approximately the 98th percentile or BMI Z-score ≥2 (ie, 2 standard deviations above the mean).

References:
1. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998; 6 Suppl 2:51S.*
2. *Hampl SE, Hassink SG, Skinner AC, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. Pediatrics 2023; e2022060640.*

OBESITY

- access to energy- dense food
- reduced physical activity
- sleep deprivation
- circadian desynchronization
- chronic stress
- anti- epileptic psychotropic drugs
- genetic and environmental factors

Obesity is associated with multiple comorbidities and complications

Metabolic, mechanical and mental

Metabolic

Mechanical

Mental

Depression

Anxiety

Asthma

NAFLD

Gallstones

Infertility

Incontinence

Arthrosis

Cancers*

Physical functioning

Sleep apnoea

CVD and risk factors
- Stroke
- Dyslipidaemia
- Hypertension
- Coronary artery disease
- Congestive heart failure
- Pulmonary embolism

Chronic back pain

Type 2 diabetes
Prediabetes

Thrombosis

Gout

CVD, cardiovascular disease; NAFLD, non-alcoholic fatty liver disease
*Including breast, colorectal, endometrial, esophageal, kidney, ovarian, pancreatic and prostate

Adapted from Sharma AM. *Obes Rev*. 2010;11:808-9; Guh *et al. BMC Public Health* 2009;9:88; Luppino *et al. Arch Gen Psychiatry* 2010;67:220–9; Simon *et al. Arch Gen Psychiatry* 2006;63:824–30; Church *et al. Gastroenterology* 2006;130:2023–30; Li *et al. Prev Med* 2010;51:18–23; Hosler. *Prev Chronic Dis* 2009;6:A48

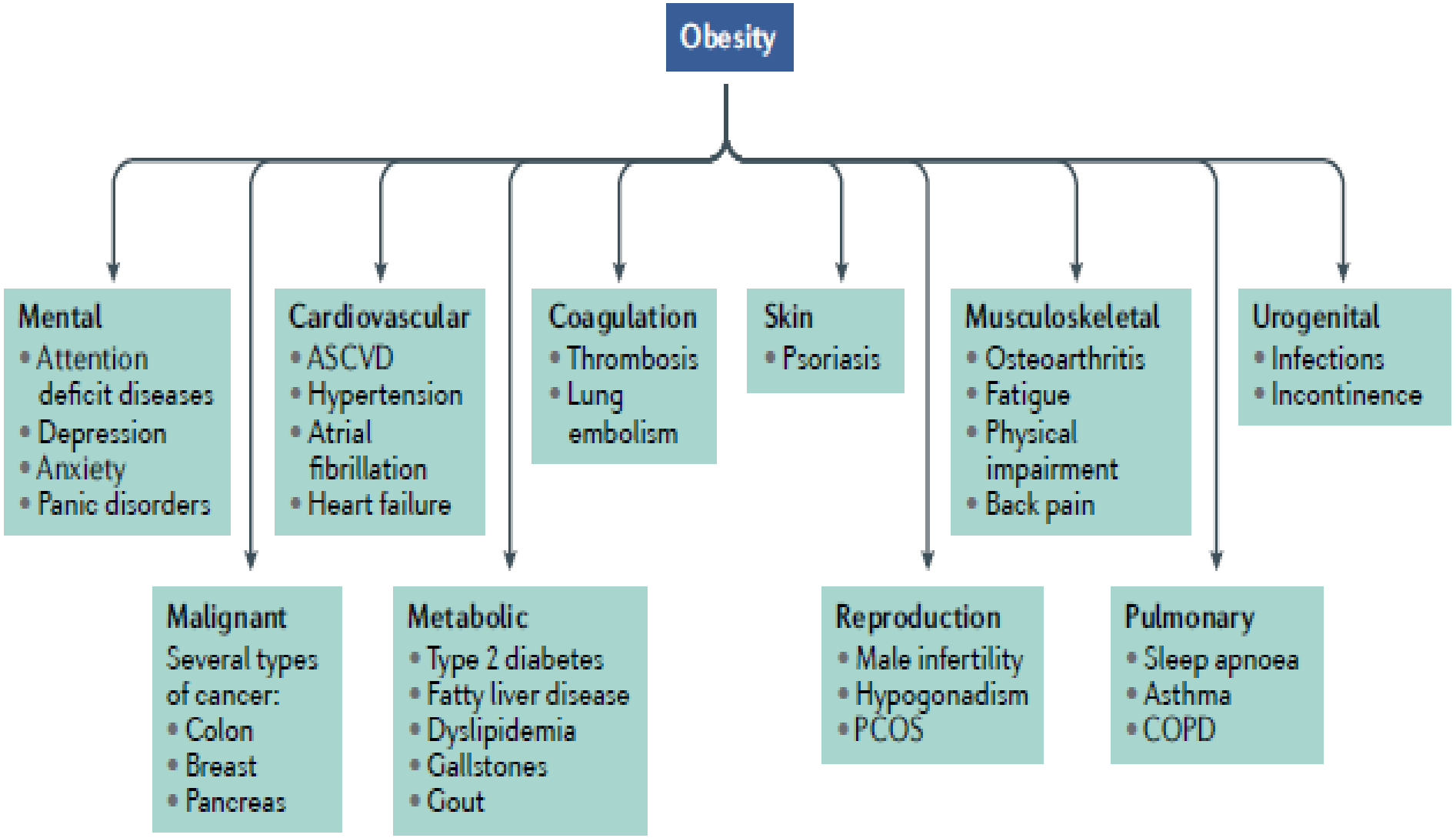


Fig. 1 | **Obesity-associated metabolic disturbances.** Most prominent metabolic and psychological comorbidities associated with morbid obesity. ASVCD, atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; PCOS, polycystic ovary syndrome.

Greater weight loss further improves obesity-related complications

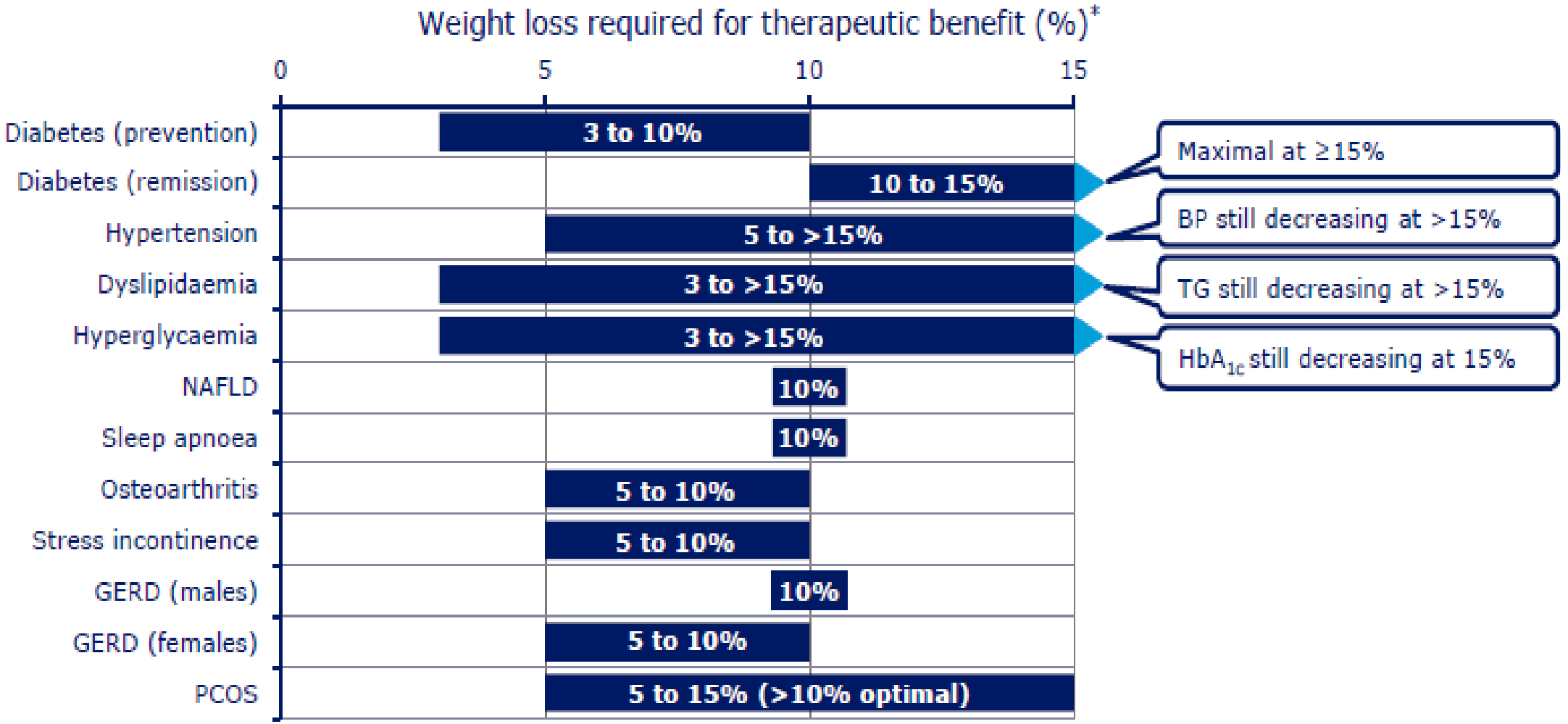
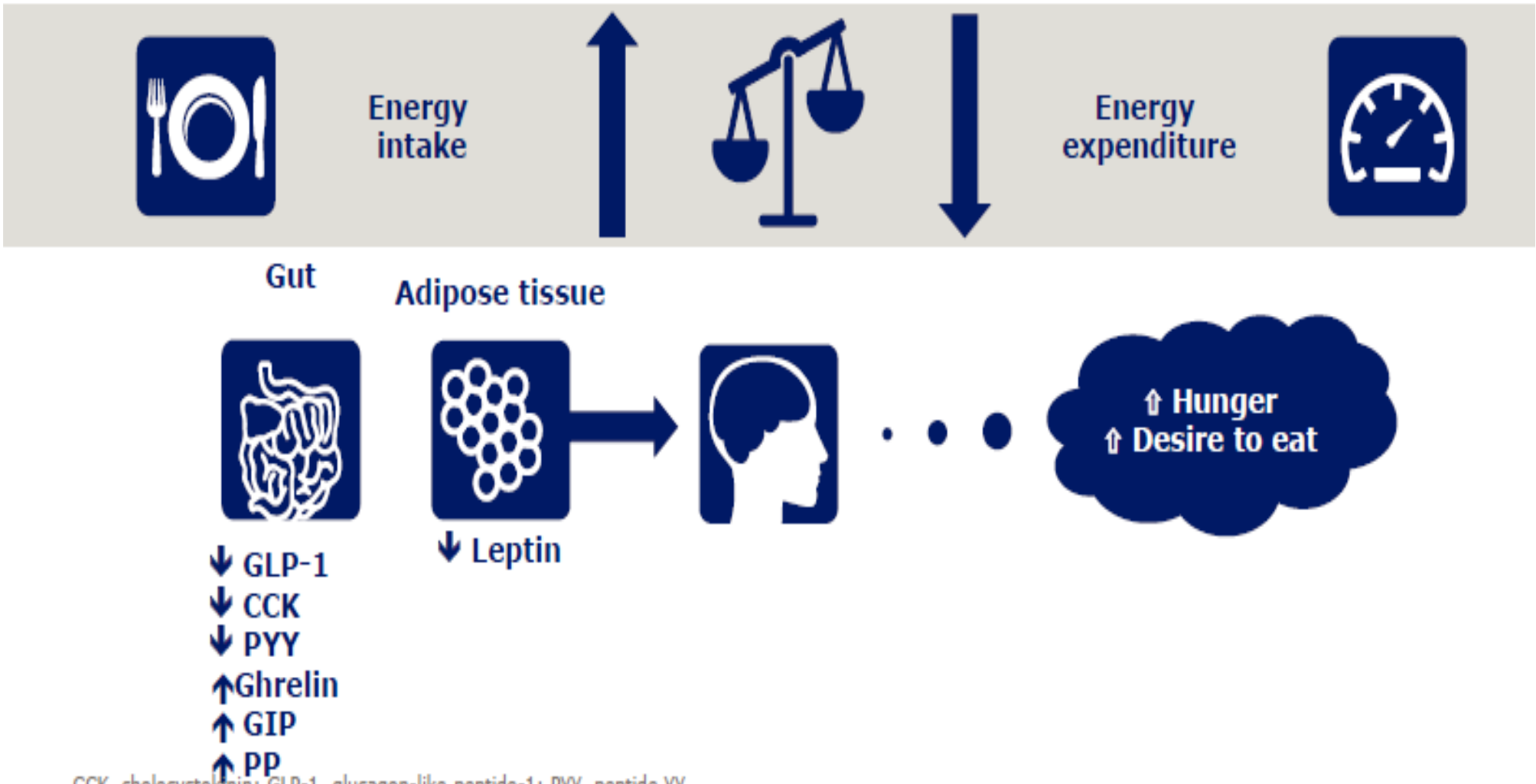


*Figure displays weight loss ranges examined in the studies (impact of >10% weight on NAFLD, and sleep apnoea symptoms was not reported). BP, blood pressure; TG, triglycerides; GERD, gastroesophageal reflux disease; NAFLD, non-alcoholic fatty liver disease; PCOS, polycystic ovary syndrome; TG, triglycerides

Cefalu *et al. Diabetes Care* 2015;38:1567–82; Lean *et al. Lancet* 2018;391:541–51

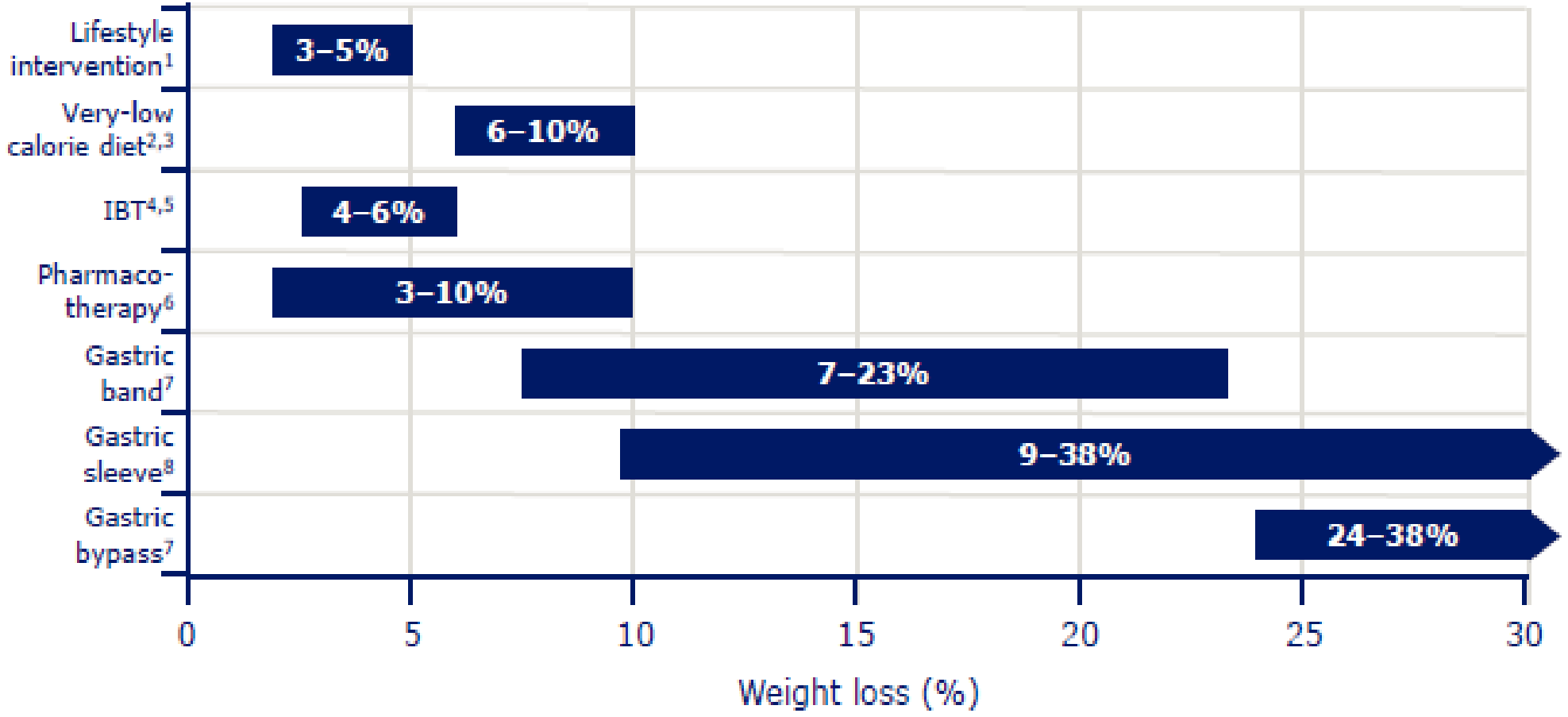
Physiological responses to weight loss favour weight regain[1,2]



CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; PYY, peptide YY

1. Schwartz *et al. Obes Rev* 2010;11:531–47; 2. Sumithran *et al. N Engl J Med* 2011;365:1597–604

Efficacy of existing weight loss interventions



1. le Roux *et al. Lancet* 2017;389:1399–409 2. Lean *et al. Lancet* 2018;391:541–51; 3. Tsai & Wadden. *Obesity* 2006;14:1283–1293; 4. Wadden *et al. Obesity* 2011;19:1987–1998; 5. Wadden *et al. Obesity* 2018; doi:10.1002/oby.22359; 6. Patel. *Metabolism* 2015;64:1376–85; 7. Courcoulas *et al. JAMA* 2013;310:2416–25; 8. Berry *et al. Obes Surg* 2018;28:649–655

GUT HORMONES

- meal-related fluctuations
- diurnal fluctuations
- circadian clock in the hypothalamic suprachiasmatic nucleus
- The most important entrainment signal of the master clock in mammals is the light–dark cycle, which inevitably determines the feeding–fasting cycle

NUTRIENTS 2021, 13, 1839. HTTPS://DOI.ORG/10.3390/NU13061839

HUNGER & SATIETY

- influenced by environmental factors such as palatability and food odour

- hedonic eating behaviour include those next to the hypothalamus and the brainstem dopaminergic brain reward centres in the mesolimbic brain region as well as the hippocampus and cortex.

https://doi.org/10.1038/s41573-021-00337-8

FASTING & FEEDING

nuclei of the hypothalamus and brain stem play an important role in the regulation of energy homeostasis.

Nutrients 2021, 13, 1839. https://doi.org/10.3390/nu13061839

SATIETY

- vagus nerve induces satiety in response to nutrients through distension

- stretch-induced meal termination

Nutrients 2021, 13, 1839. https://doi.org/10.3390/nu13061839

OBESITY & GUT HORMONES

- In obese patients, the nocturnal rise in plasma ghrelin levels is blunted.
- The amplitude of the diurnal rhythm in leptin levels is increased.
- GLP-1 levels peak during the day in humans, but the rhythmicity was also lost in obese patients.

Nutrients 2021, 13, 1839. https://doi.org/10.3390/nu13061839

BARIATRIC SURGERY & GUT HORMONES

- improvement in glucose homeostasis in patients undergoing RYGB surgery or sleeve gastrectomy is associated with elevated post prandial PYY and GLP-1 levels, even one year after surgery

- CCK-secreting cells are mainly located in the bypassed duodenum..

BARIATRIC SURGERY & GUT HORMONES

After RYGB surgery, the contact of nutrients with much of the stomach and duodenum is bypassed, resulting in a rapid delivery of undigested nutrients to the jejunum.

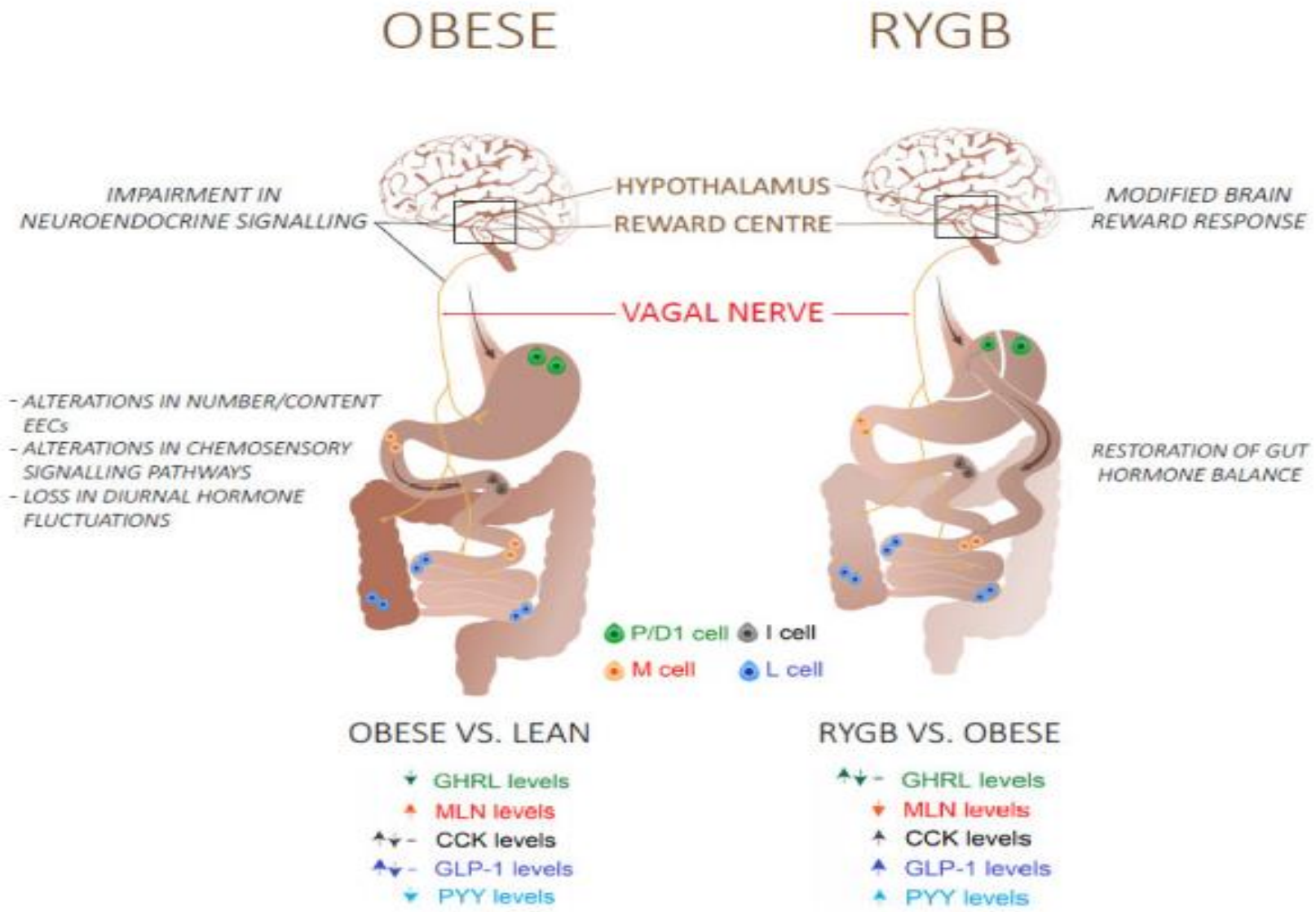


Figure 1. An overview of the mechanisms and the differences in fasting (GHRL, MLN) and postprandial (CCK, GLP-1, PYY) gut hormone plasma levels in obese/type 2 diabetes patients before and after a Roux-en-Y gastric bypass (RYGB) surgery. Abbreviations: GHRL: Ghrelin; MLN: Motilin; CCK: Cholecystokinin; GLP-1: glucagon-like peptide 1; peptide YY.

Nutrients 2021, 13, 1839. https://doi.org/10.3390/nu13061839

Table 2. An overview of several combination therapies with GLP-1R agonists that are currently in clinical trials.

Combination Therapy	Physiological Effect	Drug Candidates		
GLP-1–GIP	Insulinotropic effect Decrease food intake cardiovascular protection	Drug	Company	Status
		Tirzepatide	Eli Lilly	Phase II
GLP-1–GCG	Insulinotropic effect cardiovascular protection Decrease food intake Increase energy expenditure	Drug	Company	Status
		Cotadutide	Astrazeneca	Phase II
		Efinopegdutide	Hanmi Pharmaceuticals	Phase II
GLP-1–GCG-GIP	Insulinotropic effect Increase energy expenditure cardiovascular protection Decrease food intake	Drug	Company	Status
		MAR423	Novo-nordisk/Marcadia	Phase I
		HM15211	Hanmi Pharmacueticals	Phase II

Glucagon-like-peptide 1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), glucagon (GCG).

Nutrients 2021, 13, 1839. https://doi.org/10.3390/nu13061839

OBESITY & GI CANCER

Increases the risk of death due to cancer of the oesophagus, colon and rectum, liver, gallbladder, pancreas and kidney.

FOOD INTAKE- RELATED GUT HORMONES

- **short- term regulators of food intake:**

which are either secreted in anticipation of (ghrelin), response to (cholescystokinin (CCK), peptide tyrosine tyrosine (PYY), glucagon-like peptide 1 (GLP1), glucose- dependent insulinotropi polypeptide (GIP), oxyntomodulin (OXM)) or deprivation from (glucagon, fibroblast growth factor 21 (FGF21)

- **long- term regulators of food intake:**

which signal to the brain in proportion to the amount of fat stored in the body (leptin, insulin, amylin)

https://doi.org/10.1038/s41573-021-00337-8

FGF 21

- secreted from the liver under conditions of fasting
- decreases body weight by increasing energy expenditure via central & peripheral mechanisms.

https://doi.org/10.1038/s41573-021-00337-8

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Special Issue: *The Year in Diabetes and Obesity*
REVIEW

Gut microbiome and its role in obesity and insulin resistance

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PREBIOTIC FIBERS

fermented by the gut microbiota to short chain fatty acids (SCFAs) that act on enteroendocrine cells via FFAR2 or FFAR3 affect gut hormone release.

OBESITY & GI DISEASE

Abdominal obesity better justify the link between obesity and the complication of GERD such as **Barrett Esophagus & esophageal adenocarcinoma.**

Nutrients 2020, 12, 111; doi:10.3390/nu12010111

Table 2. Some of the mechanisms linking obesity and GI disease.

Factor	Mechanism	GI Disease	References
Mechanical	• Increase abdominal pressure • Lead to the relaxation of the lower esophageal sphincter (LES) • Increase the risk of occurrence of hiatus hernia	GERD Diverticular disease	Emerenziani S. et al., 2013 [6] Pandolfino JE et al., 2006 [7] Ze EY et al., 2017 [8] Mashayekhi R. et al., 2018 [9]
Pro tumoral	• Visceral fat releases pro-tumoral factors	GI cancer	Lauby-Secretan B. et al., 2016 [10] Larsson SC et al., 2007 [11]
Dietary factors	• Increased perception of concurrent intestinal stimuli • Modulation of intestinal motor reflexes • Inhibition of small bowel motility and delay of intestinal gas transit. • Enhanced gastro-colic reflex • Modulation of microbiota composition	IBS Functional Dyspepsia GERD	Stewart J.E., et al., 2011 [12] Cong H et al., 2018 [13]
Low-grade inflammation	• Visceral fat release of pro-inflammatory cytokines such as tumor necrosis factor and interleukins 1 and 6	IBD Pancreatitis NAFLD	Staley C, et al., 2017 [14] Kredel L. et al., 2014 [15] Khatua B. et al., 2017 [16]
Adipocytes-released peptides	• Control of GI motility	GI motor disorders	Feinle-Bisset C. et al., 2016 [17]

GERD: Gastroesophageal reflux disease, IBS: Irritable bowel syndrome, IBD: Inflammatory bowel disease, GI: Gastrointestinal, NAFLD: Nonalcoholic fatty liver disease.

Nutrients 2020, 12, 111; doi:10.3390/nu12010111

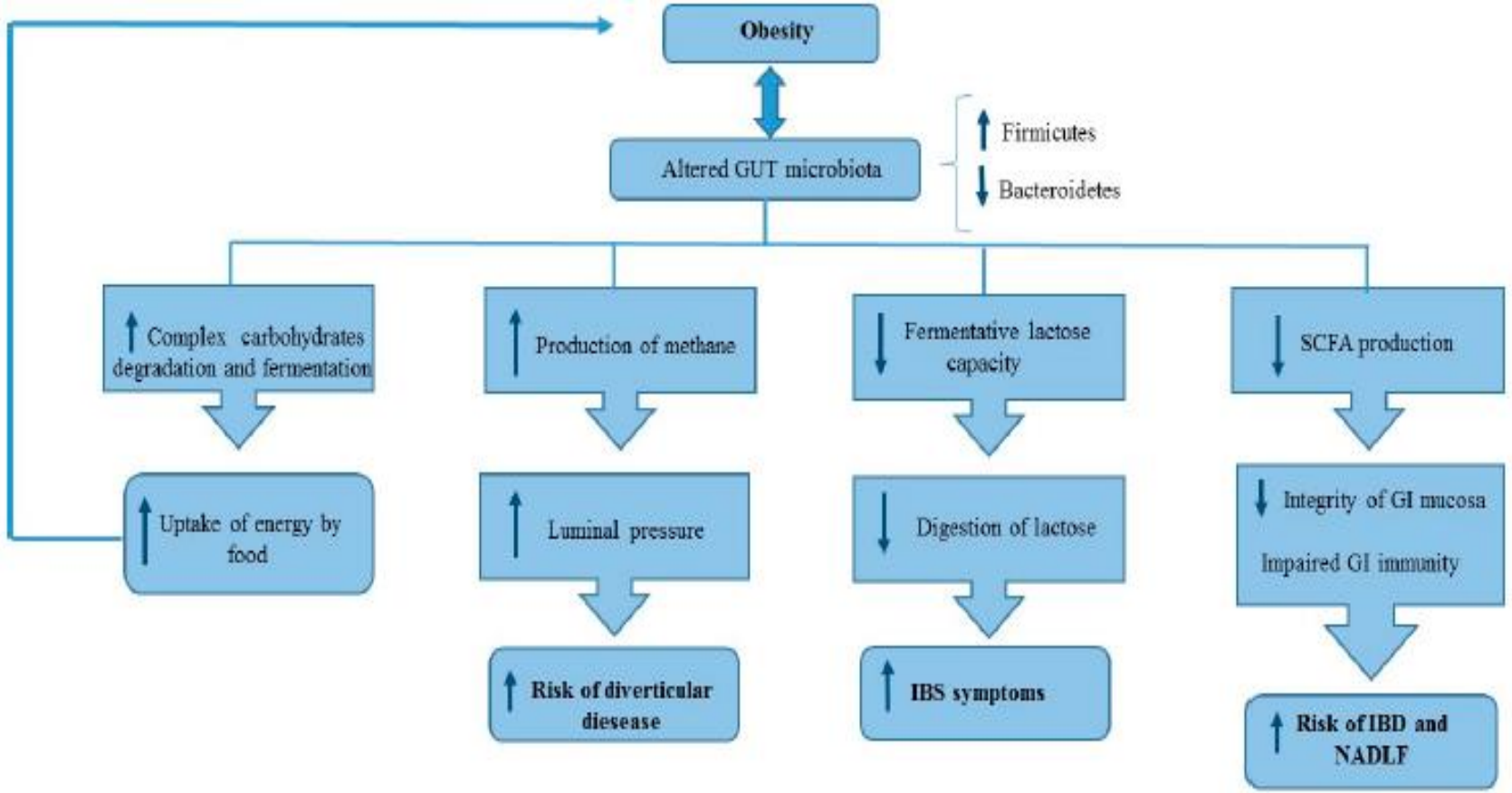


Figure 2. Relationship between altered microbiota composition and different pathophysiological mechanisms of GI disease in obese patients. SCFA: Short chain fatty acids, IBS: Irritable bowel syndrome, IBD: Inflammatory bowel disorders, NAFLD: Non-alcoholic fatty liver disease.

Nutrients 2020, 12, 111; doi:10.3390/nu12010111

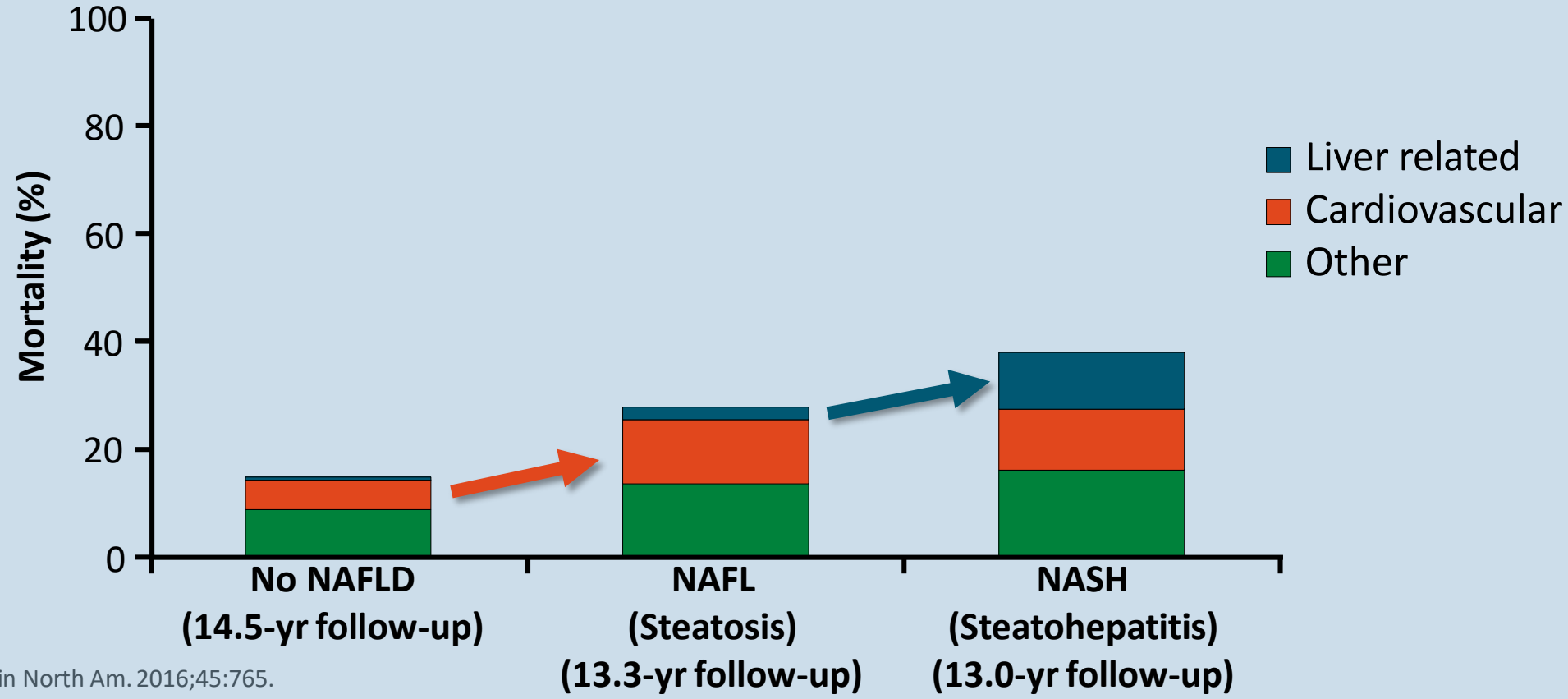
OBESITY & GI DISEASE

- GERD
- Functional dyspepsia
- Diverticulosis
- IBD
- IBS
- Pancreatitis
- NAFLD
- GI cancer

Nutrients 2020, 12, 111; doi:10.3390/nu12010111

FATTY LIVER IS NOT BENIGN: MORTALITY ASSOCIATED WITH ISOLATED STEATOSIS AND NASH

- Analysis of all-cause mortality in 6 separate studies among patients without NAFLD vs with and without NASH
  - NAFLD determined by ultrasound; NASH determined by liver biopsy



Bril. Endocrinol Metab Clin North Am. 2016;45:765.

TO SCREEN OR NOT TO SCREEN FOR NAFLD?

AASLD Guidance[1]

- **Type 2 diabetes**
  - Have high index of suspicion for NAFLD and NASH; risk stratify with NFS, FIB-4, VCTE
- **Other risk factors for NAFLD**
  - Uncertain long-term benefits, cost-effectiveness of routine screening for NAFLD

EASL-EASD-EASO Guidelines[2]

- **High CV risk**
  - Screening for NAFLD recommended

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388.

NORMAL LIVER ENZYMES DO NOT RULE OUT NASH

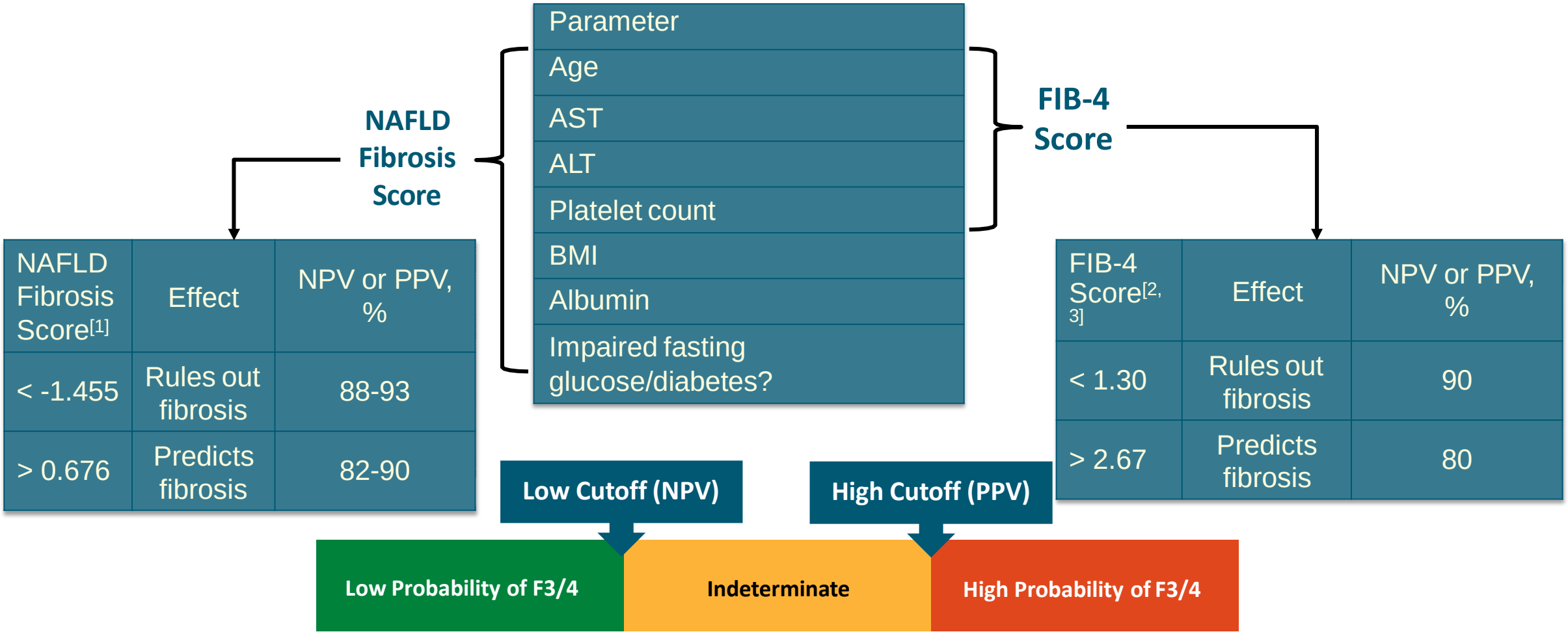
- NAFLD a common diagnosis in patients with “incidental” abnormal liver enzymes such as ALT, AST[1-3]

However:

- Liver enzymes may be normal in ~ 80% of NAFLD patients[4,5]
  - ALT and AST not sensitive for NAFLD/NASH
  - Poor correlation between ALT and histology
    - ALT typically decreases with advanced fibrosis
    - As NASH progresses, AST/ALT ratio may increase (ie, ALT < AST)
- Histology severity similar in NAFLD patients with normal vs abnormal liver enzymes[6-8]

1. Daniel. Am J Gastroenterol. 1999;94:3010. 2. Skelly. J Hepatol. 2001;35:195. 3. Pendino. Hepatology. 2005;41:1151.
4. Browning. Hepatology. 2004;40:1387. 5. Dyson. Frontline Gastroenterol. 2014;5:211. 6. Mofrad. Hepatology. 2003;37:1286.
7. Sorrentino. J Hepatol. 2004;41:751. 8. Fracanzani. Hepatology. 2008;48:792.

SCORES FOR IDENTIFYING ADVANCED FIBROSIS IN NAFLD: NAFLD FIBROSIS SCORE AND FIB-4



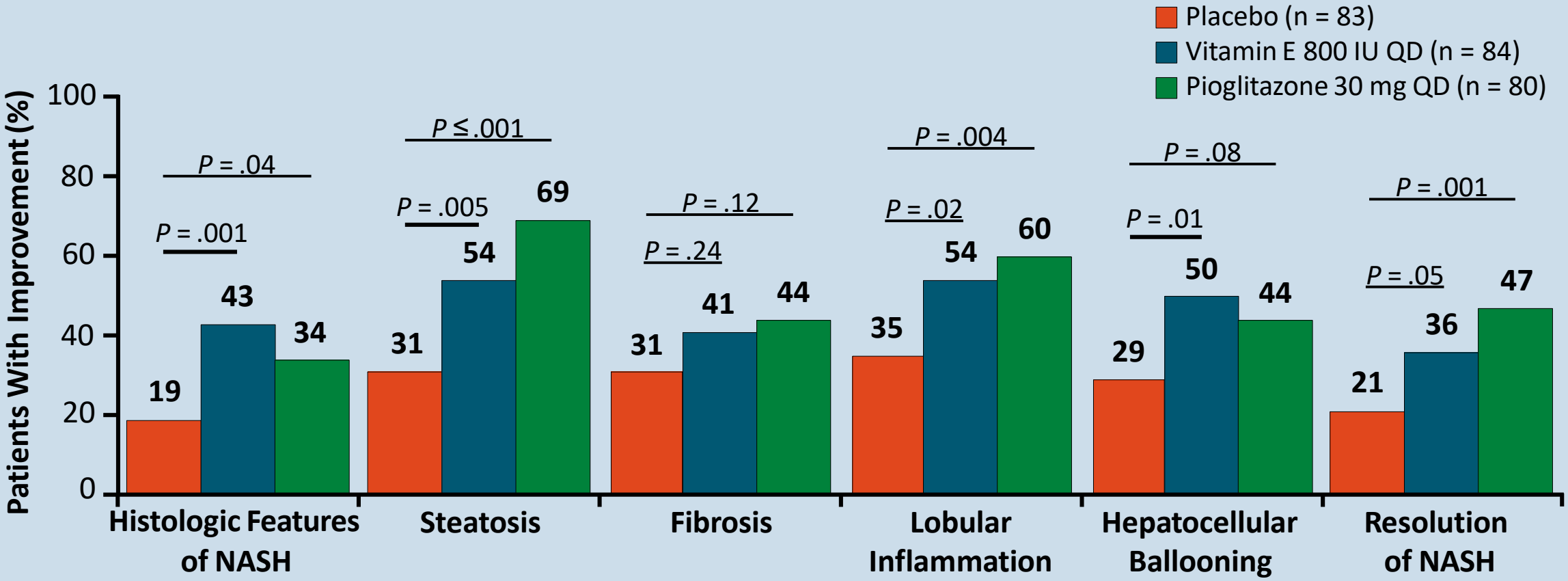
1. Angulo. Hepatology. 2007;45:846. 2. Shah. Clin Gastroenterol Hepatol. 2009;7:1104. 3. McPherson. Gut. 2010;59:1265.

TREATMENT OF NAFLD/NASH

- **Recommended Pharmacologic Therapies for NASH**
  - Pioglitazone
  - Vitamin E
- **Optimal Diabetes Therapies in NAFLD/NASH**
  - Weight Loss
  - Liver Health
- **Surgical Approaches to Weight Loss and Effect on Liver**

PIVENS: 96-WK RESULTS OF PIOGLITAZONE AND VITAMIN E IN PATIENTS WITH NASH

- Double-blind, placebo-controlled, randomized phase III study in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



Sanyal. NEJM. 2010;362:1675.

AASLD GUIDANCE: USE OF INSULIN SENSITIZERS TO TREAT NAFLD/NASH

- **Metformin**
  - Not recommended for treating NASH in adults
  - Improves serum aminotransferases and IR, but does not significantly improve liver histology
- **GLP-1 RAs**
  - It is premature to consider GLP-1 RAs to specifically treat liver disease in patients with NAFLD or NASH
- **Pioglitazone** ✓
  - With biopsy-proven NASH: improves liver histology in patients **with and without T2D**
  - Risks and benefits should be discussed with each patient
  - Without biopsy-proven NASH: should not be used for NAFLD

Chalasani. Hepatology. 2018;67:328.

AASLD GUIDANCE: VITAMIN E

- **May be considered** to treat biopsy-proven NASH in **nondiabetic** adults
- At 800 IU/day improves liver histology but not fibrosis
- Risks and benefits should be discussed with each patient
  - Long-term safety issues concerns linger (eg, impact on long-term mortality, prostate cancer)

- **Not recommended** to treat NASH in **diabetic** patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
  - More data on safety and efficacy needed

Chalasani. Hepatology. 2018;67:328.

SAFETY AND TOLERABILITY OF RECOMMENDED THERAPIES (OFF LABEL)

Vitamin E (800 IU/day)

- Possible all-cause mortality risk at > 800 IU/day[1]
- Increased hemorrhagic stroke risk[2]
  - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; *P* = .008)[3]

Pioglitazone

- Edema, weight gain (~ 2-3 kg over 2-4 yrs)[4]
- Risk of osteoporosis in women[5]
- Equivocal bladder cancer risk
  - Increased in some studies[6]
  - No association in most studies[7,8]

Use of these agents should be personalized for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio

1. Miller. Ann Intern Med. 2005;142:37. 2. Schurks. BMJ. 2010;341:c5702. 3. Klein. JAMA. 2011;306:1549.
4. Bril. Diabetes Care. 2017;40:419. 5. Yau. Curr Diab Rep. 2013;13:329. 6. Tuccori. BMJ. 2016;352:i1541.
7. Lewis. JAMA. 2015;314:265. 8. Davidson. Diabetes Complications. 2016;30:981.

APPROACHES FOR CURRENTLY AVAILABLE TREATMENTS

Weight loss[1-3]

- Lifestyle (diet, physical activity)
- Weight loss medications
- Bariatric surgery

In patients with advanced liver disease, choose or dose drugs appropriately.

Treat T2D and CV risk factors[4,5]

- Hyperglycemia (GLP-1 RA and/or SGLT-2i)
- Hypertension
- Dyslipidemia*

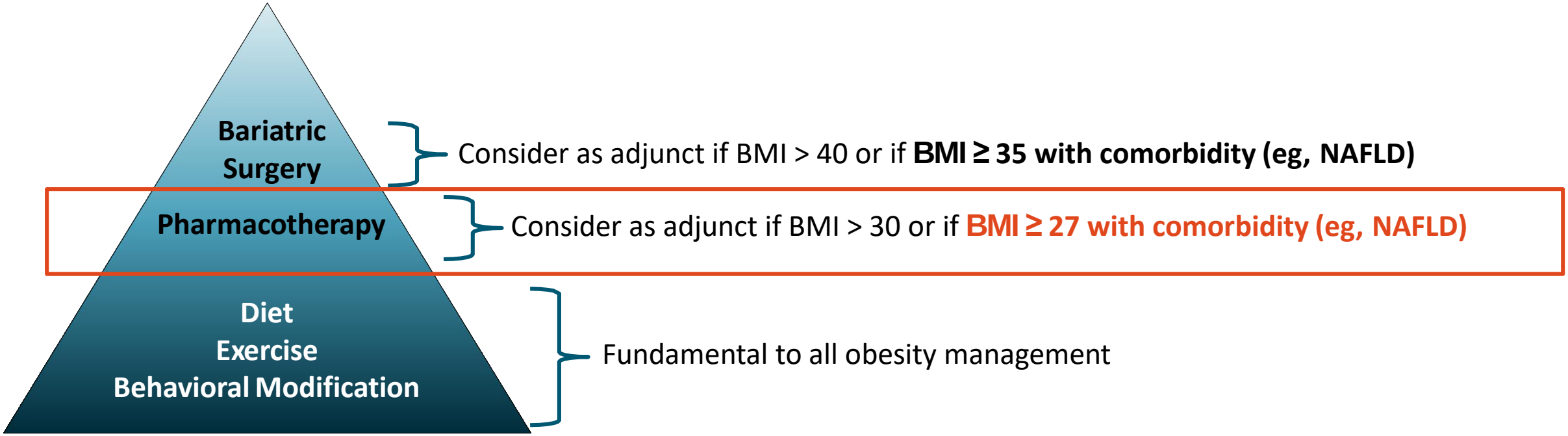
*NAFLD does not increase statin risk of drug-induced liver injury.[8]

Liver-directed treatment

- Vitamin E (except in diabetes)[6]
- Pioglitazone[6,7]

1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Sanyal. NEJM. 2010;362:1675. 7. Cusi. Ann Intern Med. 2016;165:305. 8. Bril. J Clin Endocrinol Metab. 2017;102:2950.

WEIGHT LOSS: ENDOCRINE SOCIETY 2015 OBESITY GUIDELINES

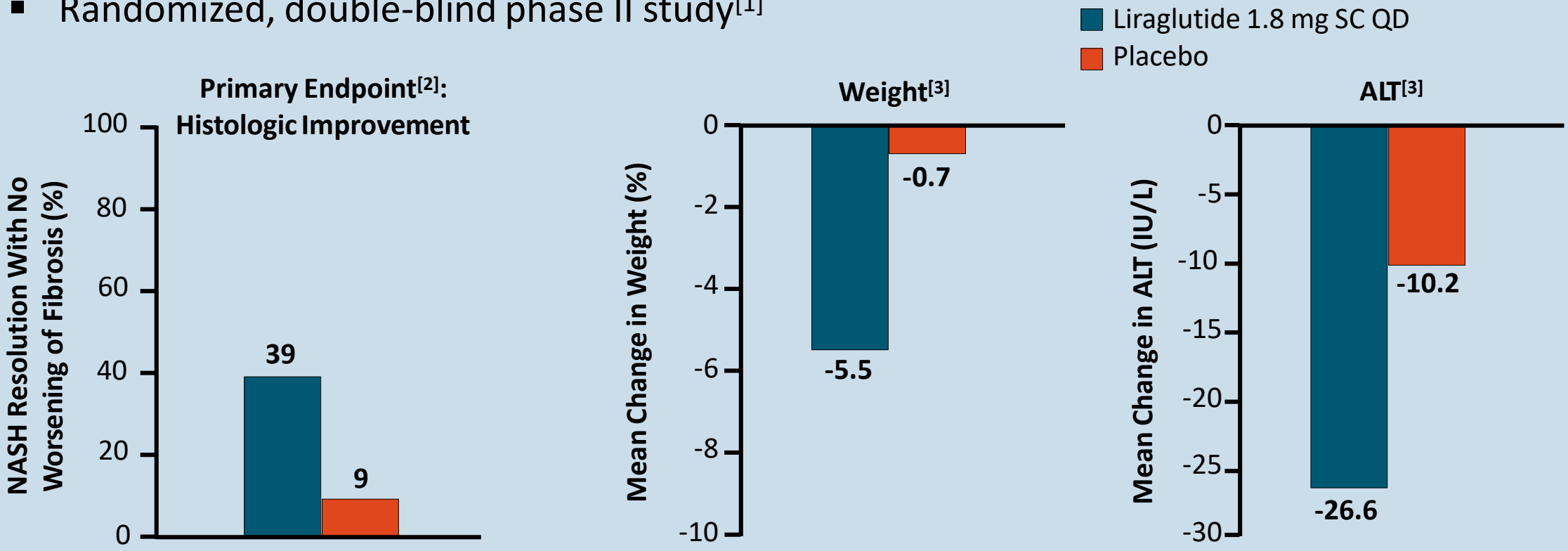


" . . . we suggest the use of approved weight loss medication (over no pharmacologic therapy)"

Apovian. J Clin Endocrinol Metab. 2015;100:342.

LEAN: 48-WK RESULTS OF LIRAGLUTIDE VS PLACEBO IN OVERWEIGHT PATIENTS WITH NASH

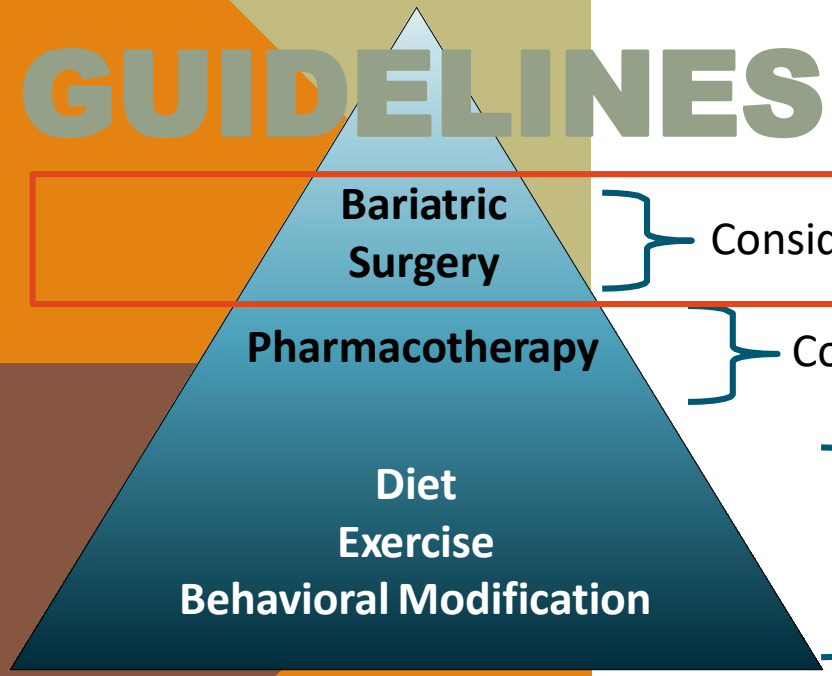
- Randomized, double-blind phase II study[1]



- Semaglutide also associated with ALT reduction and weight loss in nondiabetic adults with NASH and obesity[3]

1. Armstrong. BMJ Open. 2013;3:e003995. 2.Armstrong. Lancet. 2016;387:679. 3. Armstrong. EASL 2015. Abstr G01.

WEIGHT LOSS: ENDOCRINE SOCIETY 2015 OBESITY GUIDELINES



Consider as adjunct if BMI > 40 or if **BMI ≥ 35 with comorbidity (eg, NAFLD)**

Consider as adjunct if BMI > 30 or if **BMI ≥ 27 with comorbidity (eg, NAFLD)**

Fundamental to all obesity management

" . . . we suggest the use of approved weight loss medication (over no pharmacologic therapy)"

- Apovian. J Clin Endocrinol Metab. 2015;100:342.

ENDOSCOPIC WEIGHT LOSS DEVICES AND PROCEDURES

- Several varieties approved or in development
  - Gastric balloon systems
  - Gastric emptying systems
  - Endoscopic sleeve gastroplasty
  - Duodenal-jejunal bypass sleeves
- Current guidelines do not address these methods

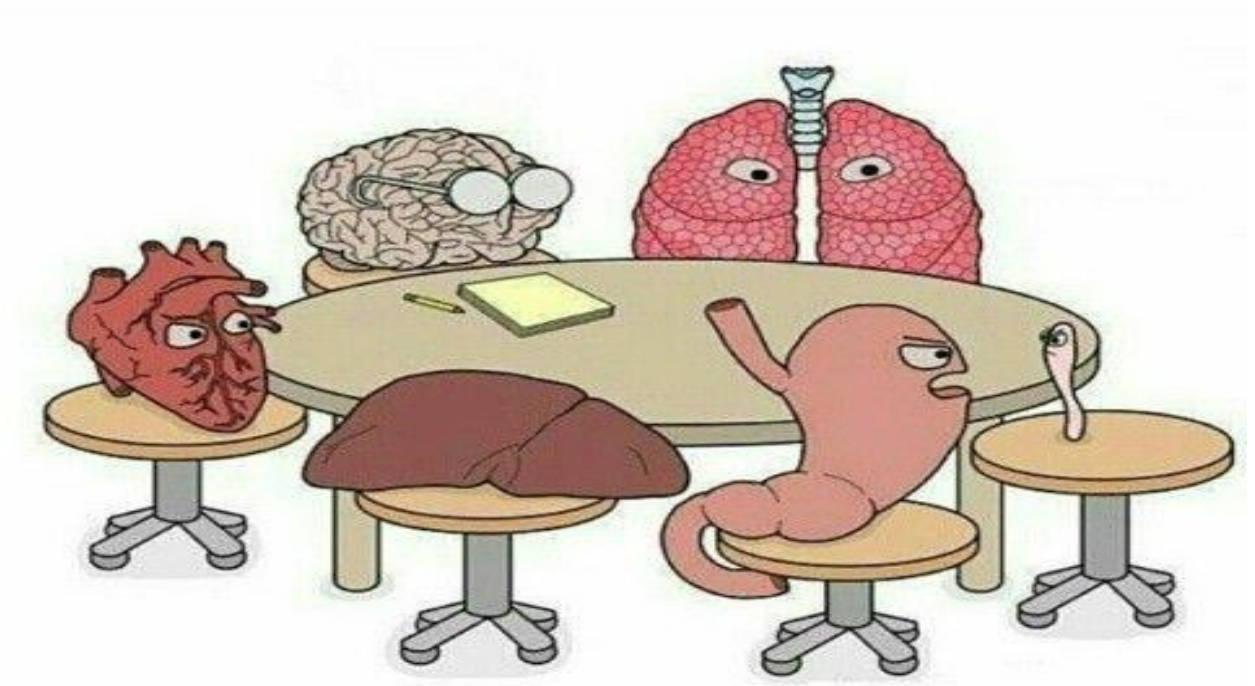
- Not widely available
- Some small studies specifically address NAFLD
  - ⊣Improved biochemical or histologic measures consistent with weight loss
- Could consider in patients who refuse pharmacologic or surgical approaches

1. Popov. Obesity Week. 2014. 2. Lee. Gastrointest Endosc. 2012;76:756.
3. Imaz. Obes Surg. 2008;18:841. 4. de Jonge. Clin Gastroenterol Hepatol. 2013;11:1517.

AASLD GUIDANCE: BARIATRIC SURGERY

- Can be considered in otherwise eligible obese individuals with NAFLD or NASH
  - Premature to consider bariatric surgery as an established option to treat NASH
- The type, safety, and efficacy of bariatric surgery are not established in obese individuals with cirrhosis from NAFLD
- In patients with compensated NASH or cryptogenic cirrhosis, bariatric surgery may be considered on a case-by-case basis by an experienced bariatric surgery program

Chalasani. Hepatology. 2018;67:328.



Thanks for your attention