

Nodi ed intrecci di una rete:

evidenze scientifiche ed esperienze a confronto



Hotel La Principina
Grosseto, 30 novembre/1 dicembre 2018



Diabesità: integrazione tra terapia medica e terapia chirurgica

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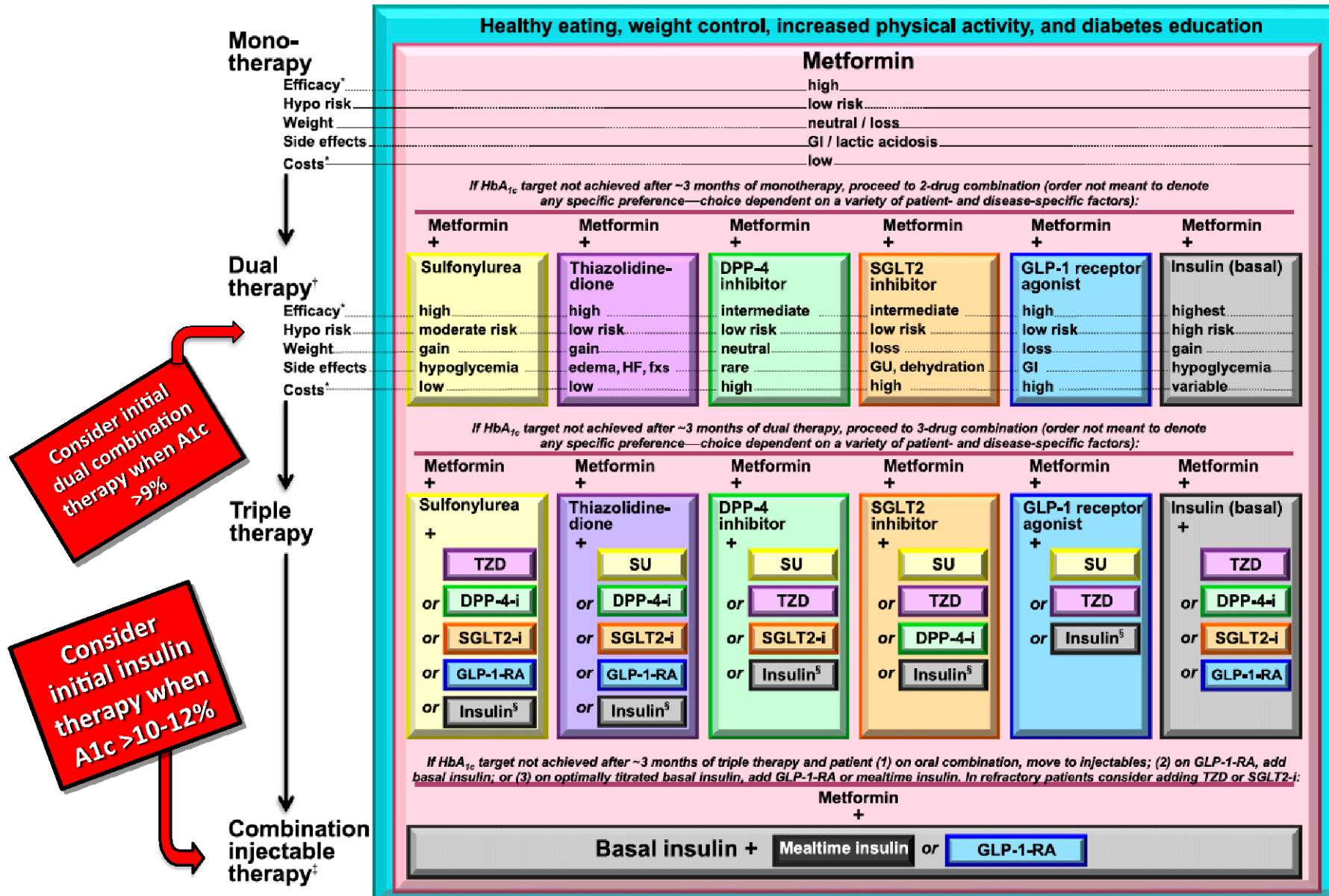


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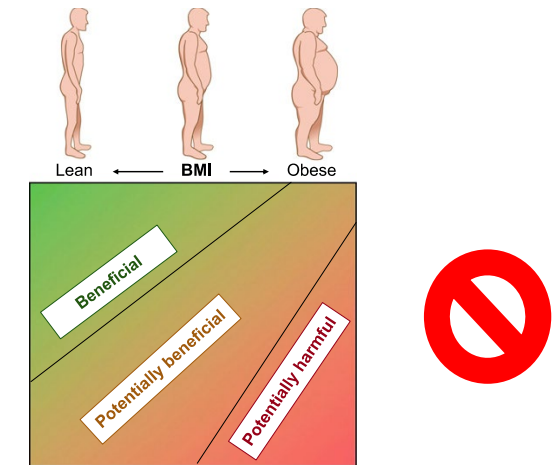


Dichiaro di non avere alcun conflitto d'interesse

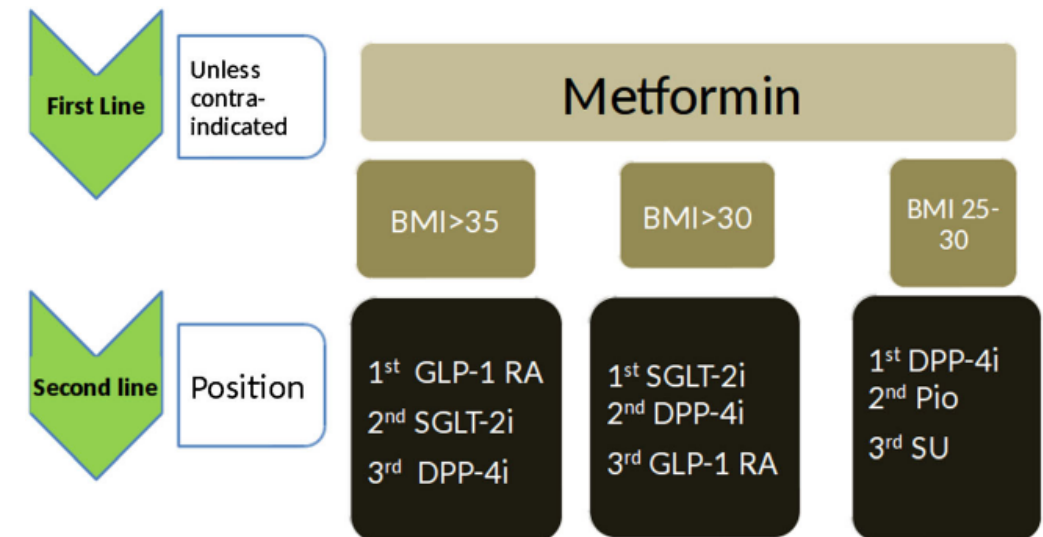
Medical Management of Diabetes



Medical Management of Diabetes: Do We Have Realistic Targets?



Algorithm for glycemic management in patients with diabetes.



American Diabetes Association 2015

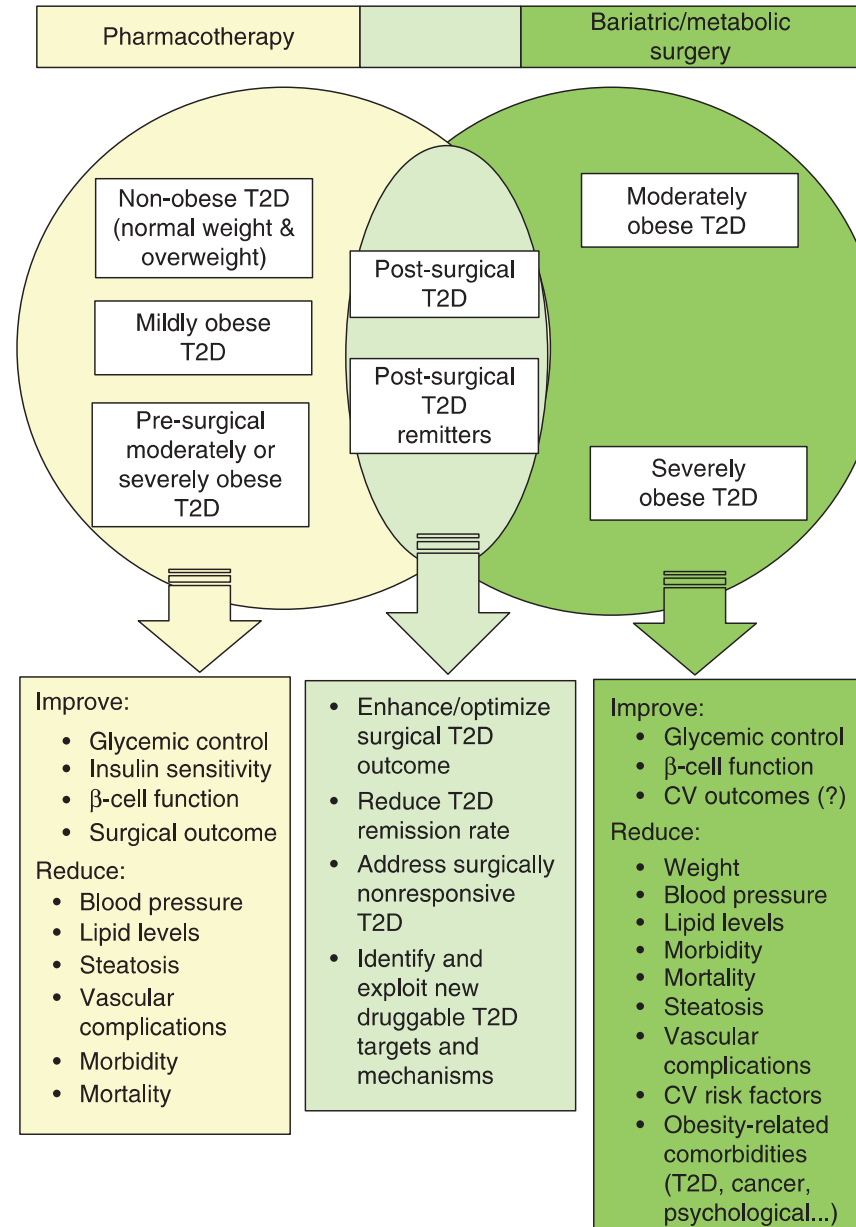
Prevention or Delay of Type 2 Diabetes

Diabetes Care 2015;38(Suppl. 1):S31–S32 | DOI: 10.2337/dc15-S008

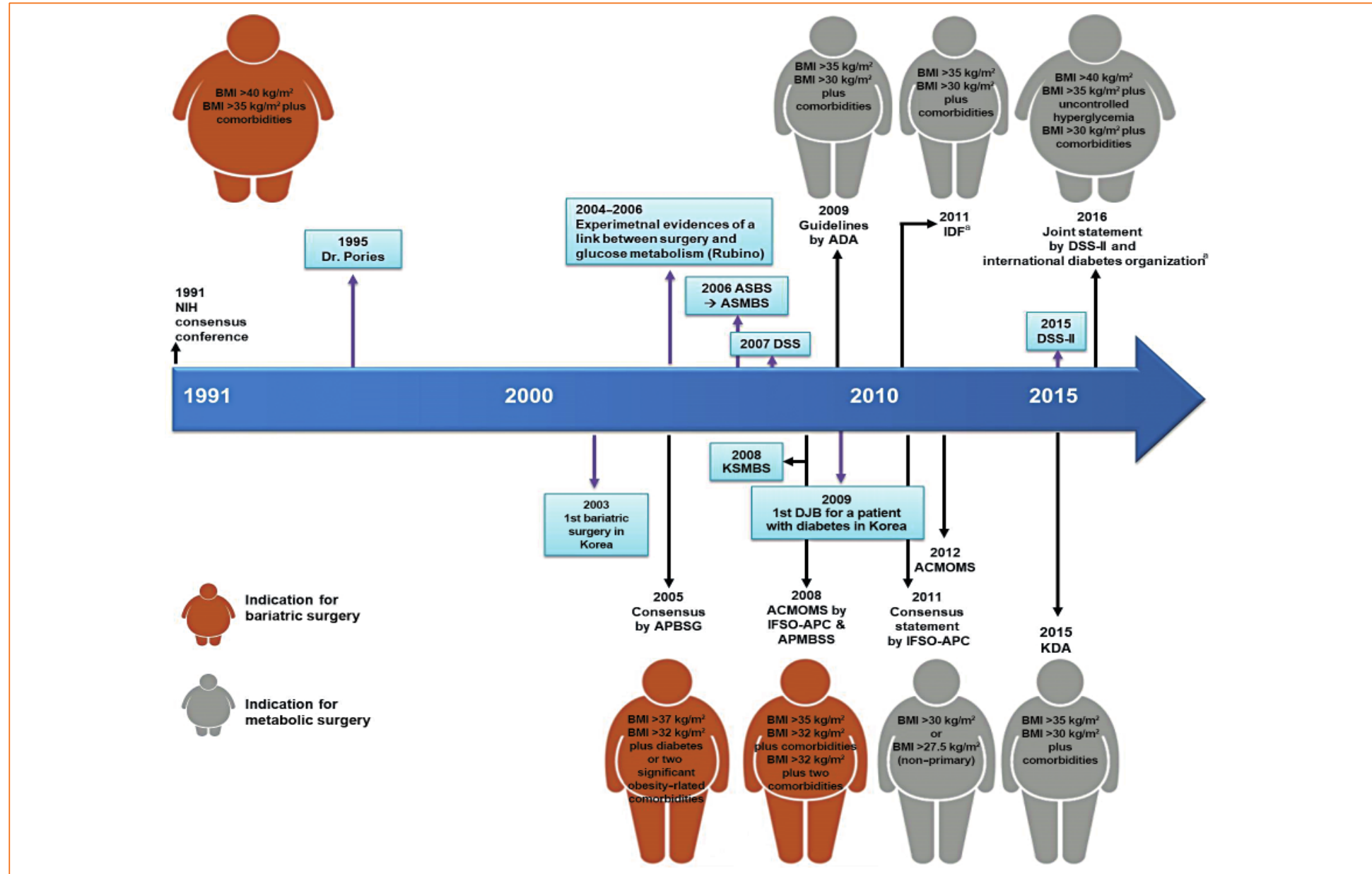
Recommendations

- Patients with impaired glucose tolerance (IGT) **A**, impaired fasting glucose (IFG) **E**, or an A1C 5.7–6.4% **E** should be referred to an intensive diet and physical activity behavioral counseling program targeting loss of 7% of body weight and increasing moderate-intensity physical activity (such as brisk walking) to at least 150 min/week.
- Follow-up counseling may be important for success. **B**
- Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. **B**
- Metformin therapy for prevention of type 2 diabetes may be considered in those with IGT **A**, IFG **E**, or an A1C 5.7–6.4% **E**, especially for those with BMI >35 kg/m², aged <60 years, and women with prior gestational diabetes mellitus (GDM). **A**
- At least annual monitoring for the development of diabetes in those with prediabetes is suggested. **E**
- Screening for and treatment of modifiable risk factors for cardiovascular disease is suggested. **B**
- Diabetes self-management education (DSME) and support (DSMS) programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes. **C**

A pharmaco-surgical interactome for T2D management.



A history of bariatric and metabolic surgery



American Diabetes Association 2018

BARIATRIC SURGERY

Recommendations

- Bariatric surgery may be considered for adults with BMI >35 kg/m² and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. **B**
- Patients with type 2 diabetes who have undergone bariatric surgery

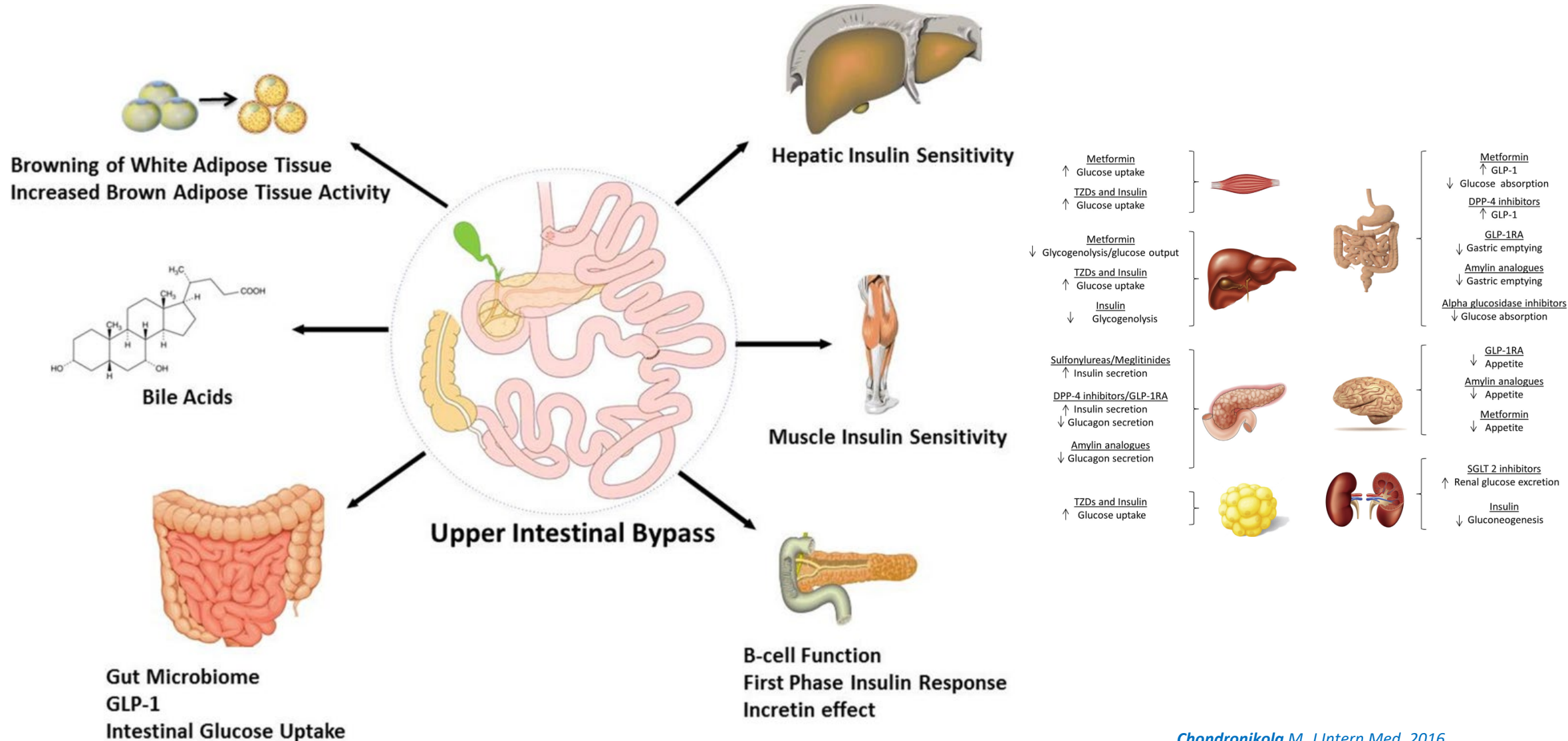
need lifelong lifestyle support and medical monitoring. **B**

- Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m², there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m². **E**

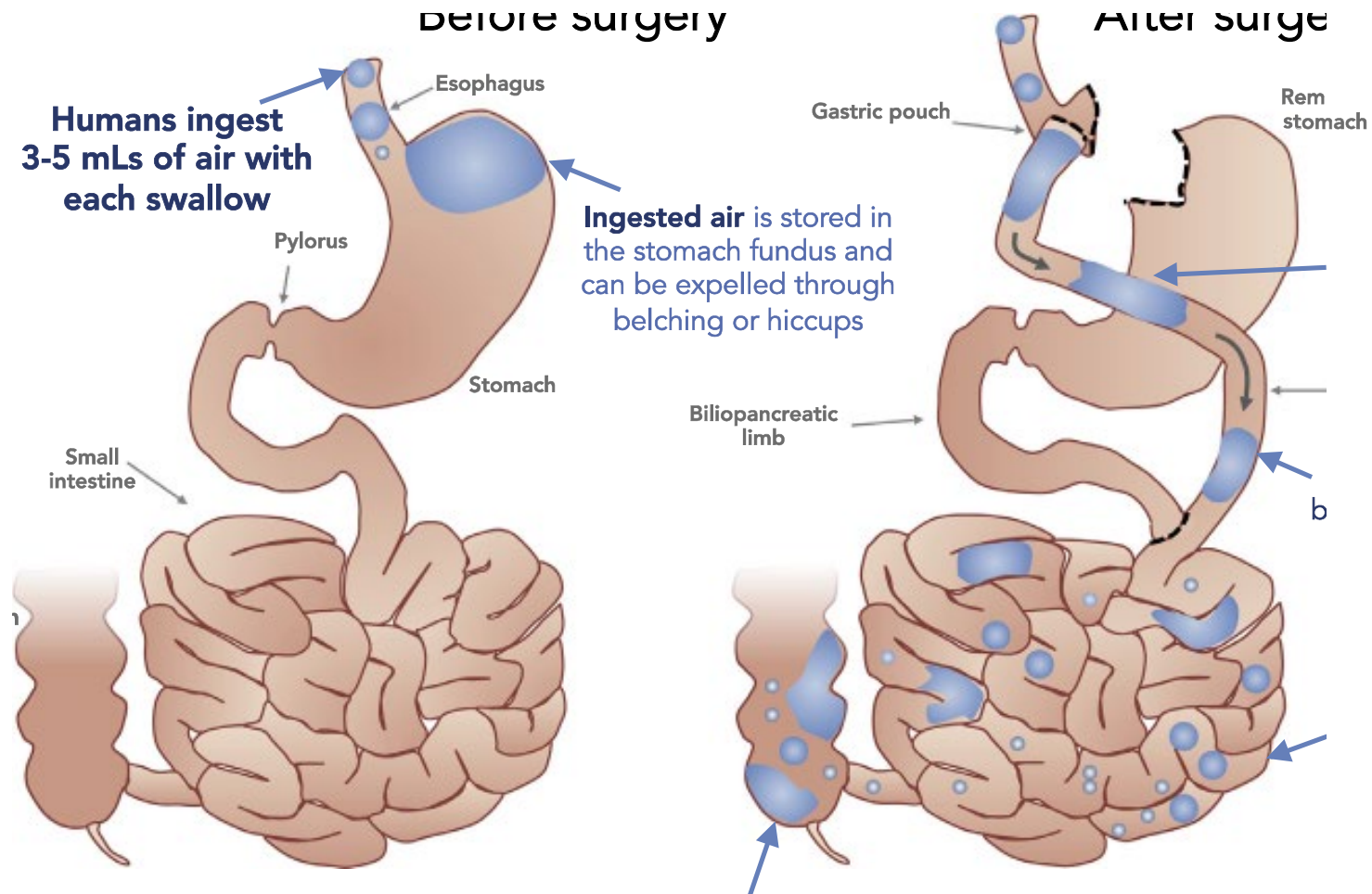
Metabolic risk score established by interassociation guideline carried out by the Brazilian Society of Metabolic and Bariatric Surgery (SBCBM), Brazilian College of Surgeons (CBC) and Brazilian College of Digestive Surgery (CBCD)

METABOLIC RISK SCORE	
Mandatory indicators	T2DM diagnosis
	Age between 30-65 years
	BMI ≥ 30 kg/m2
	Peptide C baseline >1 ng/dL and anti-GAD negative
	Glycated hemoglobin 2 points above the reference value method, despite regular medical treatment.
	Surgical indication countersigned by the multidisciplinary team
Additional indicators	BMI: 30 to 30.9 kg/m2: 0 points
	31 to 31.9 kg/m2: + 1 point
	32 to 32.9 kg/m2: + 2 points
	33 to 33.9 kg/m2: + 3 points
	34 to 34.9 kg/m2: + 4 points
	Albuminuria> 30 mg/g of creatinine in isolated sample: + 1 point
	Peptide C after mixed meal test higher than 50% from baseline: +1 point
	Hypertension: + 1 point
	Dyslipidemia: + 1 point
	Macrovascular disease evidence: + 1 point
	Non-alcoholic fatty liver disease: + 1 point
	Proven sleep apnea: + 1 point
	Diabetic duration: 2-5 years: + 2 points
	5-10 years: +1 point
	> 10 years: -1 point (negative)
	> 15 years - 2 points (negative)
	Use of insulin > 5 years: -1 point (negative)
It is understood that to have surgical indication, the patient must meet all mandatory criteria, with the total equal to or greater than 7 points of complementary indicators. The gastrojejunal bypass in Y-Roux-en-Y will be the indicated technique, except before contraindications, whereupon the vertical gastrectomy should be considered.	

Mechanisms involved in the remission of type 2 diabetes in patients who have had upper gastrointestinal bypass surgery. GLP-1, glucagon-like peptide-1.



RYGB Air Hypothesis.



Definition for Remission of Type 2 Diabetes

Table 1—Summary of consensus definitions and recommendations

Definitions

Partial remission

- Hyperglycemia below diagnostic thresholds for diabetes
- At least 1 year's duration
- No active pharmacologic therapy or ongoing procedures

HbA1c < 6.5%
Glycemia 100-125 mg/dl

Complete remission

- Normal glycemic measures
- At least 1 year's duration
- No active pharmacologic therapy or ongoing procedure

HbA1c < 6.0%
Glycemia < 100 mg/dl

Prolonged remission

- Complete remission of at least 5 years' duration

Recommendations

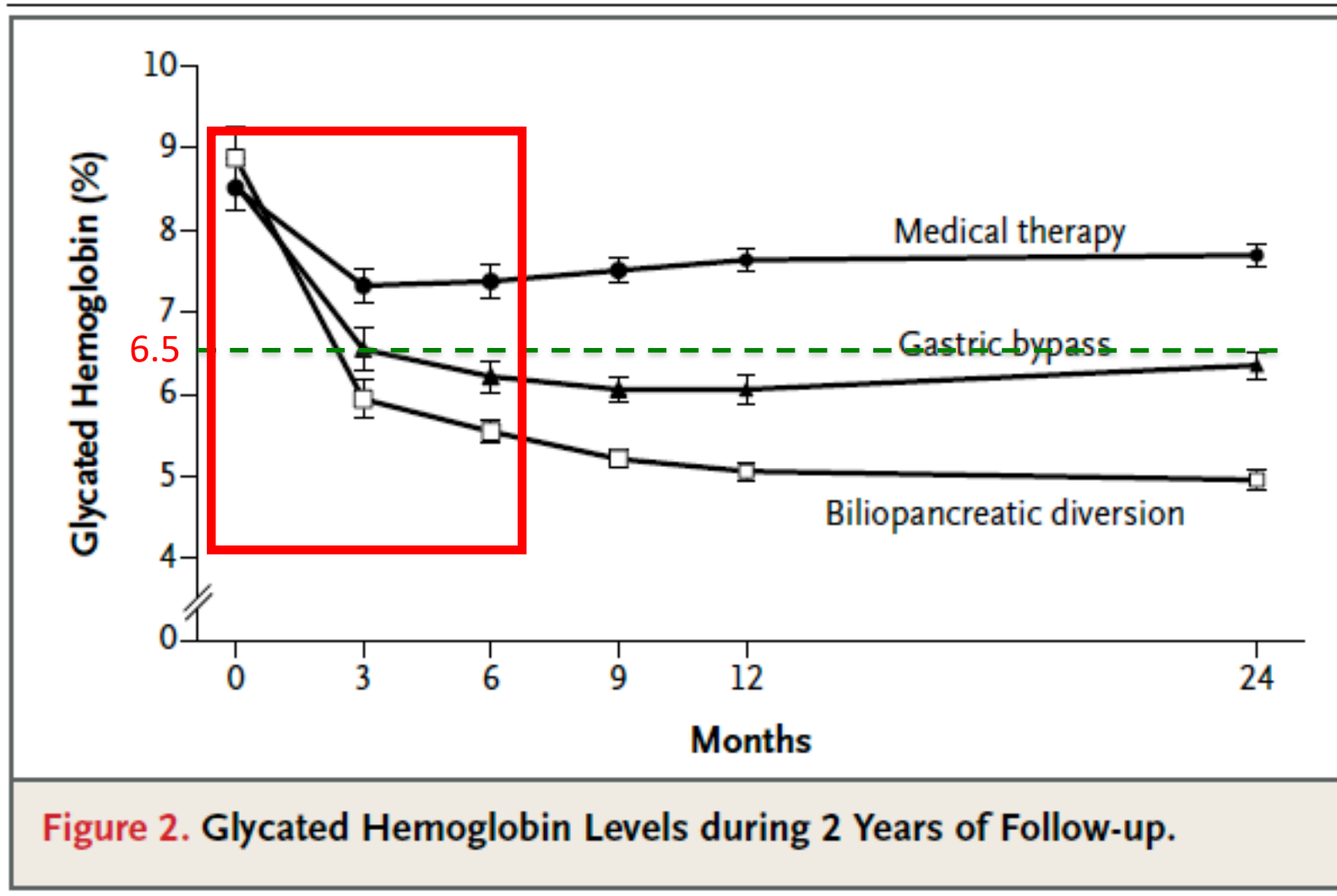
Treatment goals for comorbid conditions

- Same as those for patients with diabetes for patients with partial or complete remission of less than 5 years' duration
- With prolonged remission, could consider goals appropriate for patients without diabetes, as long as there is no recurrence of diabetes and no cardiovascular disease

Screening for microvascular complications

- Same protocols as those for patients with diabetes for patients with partial or complete remission of less than 5 years' duration
- With prolonged remission, could consider screening at reduced frequency depending on the status of each complication
- With prolonged remission, only consider stopping screening for a particular complication completely if there is no history of that complication

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

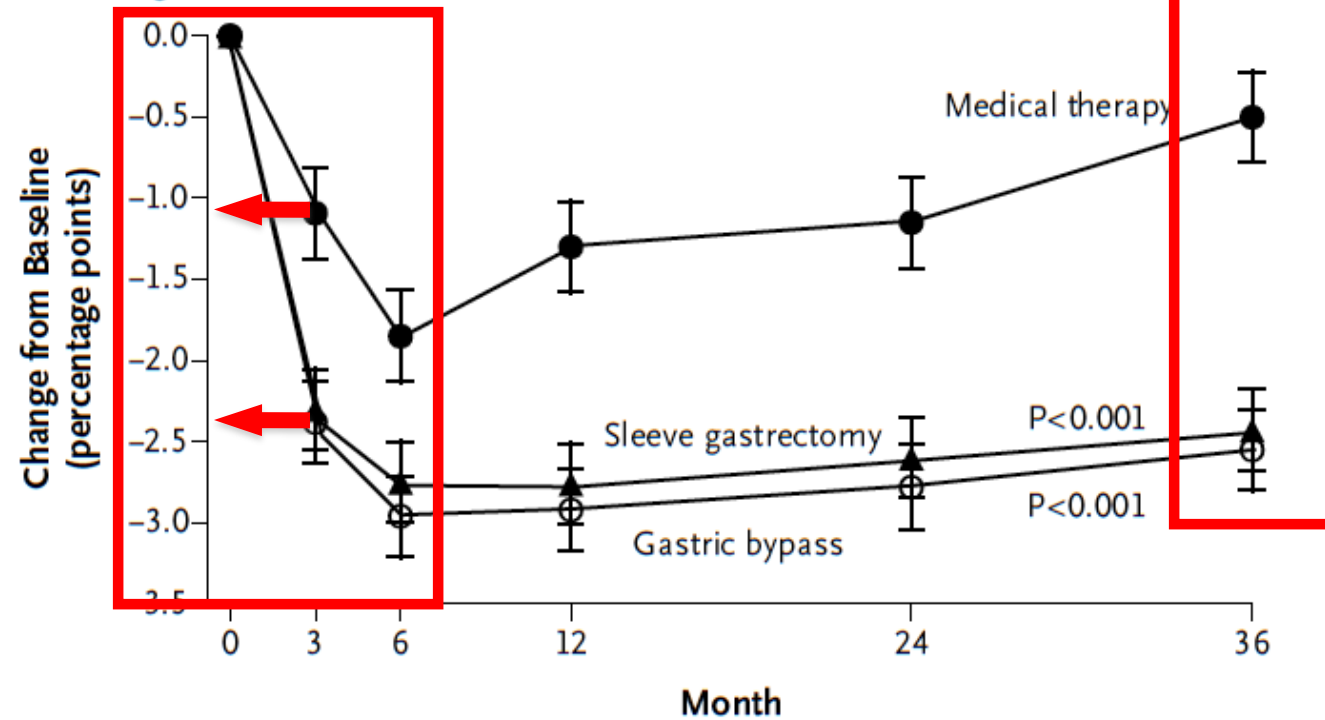


ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes

Schauer PR, et al 2014

Glycated Hemoglobin



Value at Visit

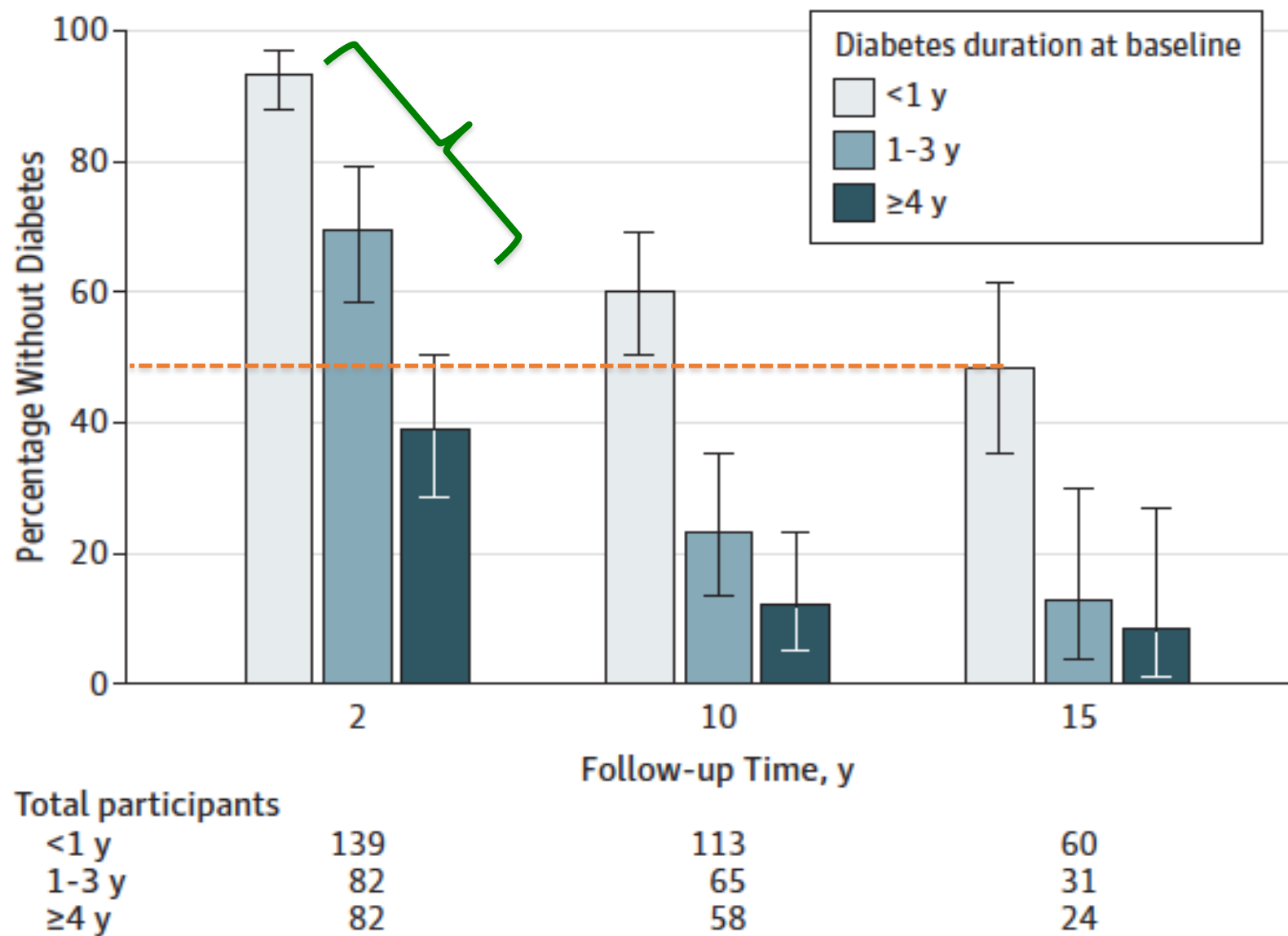
Medical therapy	9.0 (8.5)	7.1 (6.8)	7.5 (6.9)	7.7 (7.3)	8.4 (7.6)
Sleeve gastrectomy	9.5 (8.9)	6.7 (6.4)	6.6 (6.4)	6.8 (6.8)	7.0 (6.6)
Gastric bypass	9.3 (9.2)	6.3 (6.2)	6.3 (6.1)	6.5 (6.4)	6.7 (6.6)

Retrospective studies that have assessed diabetes remission rates according to ADA criteria

Author, year	Procedure	Follow up	Number	Remission rates (%)	
				Complete	Partial
Pouranas <i>et al.</i> , 2012	RYGB, VSG, BPD	23 months	209	34	NR
Ramos-Levi <i>et al.</i> , 2013	RYGB, VSG, BPD	1-year	125	36	NR
Ramos-Levi <i>et al.</i> , 2013	RYGB, VSG, BPD	1-year	141	53	NR
Ramos-Levi <i>et al.</i> , 2013	RYGB, VSG, BPD	18 months	110	50	13
Brethauer <i>et al.</i> , 2013	RYGB, VSG, BPD	5-6 years	217	24	26
Miras <i>et al.</i> , 2014	RYGB, LGB, VSG, BPD - DS	1-2 years	90	38	52
Boza <i>et al.</i> , 2014	RYGB	3 years	94	53	10

RYGB: Roux-en-Y gastric bypass, VSG: Vertical sleeve gastrectomy, LGB: Laparoscopic gastric band, BPD: Bilio-pancreatic diversion, BPD-DS: Biliopancreatic diversion with duodenal switch, NR: Not reported/retrievable, ADA: American diabetes association

Figure 2. Diabetes Remission by Diabetes Duration in the Surgery Group



Prediction score for diabetes remission

	Values
Preoperative prediction factors	
T2D duration (years)	
<1	0
1 to <3	1
3 to <5	2
5 to <7	3
≥7	4
Number of antidiabetic medications*	
0	0
1	1
2	3
≥3	4
HbA _{1c} (%)†	
<6.3	0
6.3 to <6.9	1
≥6.9	3
Postoperative (1-year) prediction factors	
Number of antidiabetic medications*	
0	0
1	1
≥2	4
Fasting blood glucose (mmol/L)	
<4.8	0
4.8 to <5.3	1
5.3 to <5.8	2
≥5.8	3
Body weight lost from baseline (%)‡	
<−34	0
−34 to <−25	1
−25 to <−20	2
≥−20	3
1-year remission status§	
DR	0
PDR	3
NDR	5
Overall score (sum of the 7 factors)	0–26
≤11 predicts long-term remission	
≥18 predicts long-term nonremission	



Preoperative Low Energy Diet Diminishes Liver Size

Robert J. Fris, MB ChB, FRCSC, FACS

Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging¹⁻³

Susan L Colles, John B Dixon, Paul Marks, Boyd J Strauss, and Paul E O'Brien

OBES SURG (2011) 21:345-350
DOI 10.1007/s11695-010-0337-2

CLINICAL RESEARCH

Preoperative 4-Week Low-Calorie Diet Reduces Liver Volume and Intrahepatic Fat, and Facilitates Laparoscopic Gastric Bypass in Morbidly Obese

David Edholm • Joel Kullberg • Arvo Haenni •
F. Anders Karlsson • Anders Ahlström •
Jakob Hedberg • Håkan Ahlström • Magnus Sundbom

Preoperative Very Low-Calorie Diet and Operative Outcome After Laparoscopic Gastric Bypass

A Randomized Multicenter Study

Yves Van Nieuwenhove, MD, PhD; Zilvinas Dambrauskas, MD, PhD; Alvaro Campillo-Soto, MD;
Francois van Dielen, MD, PhD; René Wiezer, MD; Ignace Janssen, MD;
Michael Kramer, MD; Anders Thorell, MD, PhD

Arch Surg. 2011;146(11):1300-1305

Conclusions: Although weight reduction with a 14-day VLCD regimen before laparoscopic gastric bypass performed in high-volume centers seems to reduce the perceived difficulty of the procedure, only minor effects on operating time, intraoperative complications, and short-term weight loss could be expected. However, the finding of reduced postoperative complication rates suggests that such a regimen should be recommended before bariatric surgery.

[Surg Obes Relat Dis.](#) 2015 May-Jun;11(3):578-84. doi: 10.1016/j.soard.2014.11.004. Epub 2014 Nov 13.

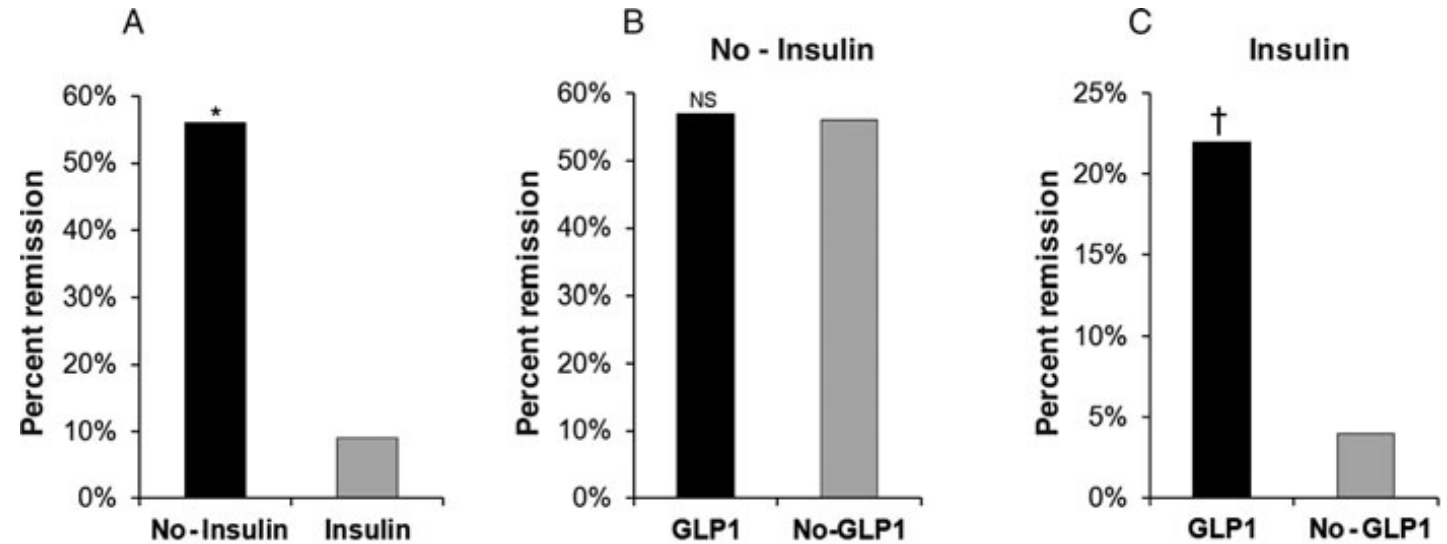
Impact of perioperative management of glycemia in severely obese diabetic patients undergoing gastric bypass surgery.

[Chuah LL](#)¹

CONCLUSIONS:

Our pilot studies suggested that neither intensive management of glycemia in the 3 months pre- RYGB, nor the first 2 weeks post-RYGB resulted in better glycemic control one year after surgery. RYGB has substantial effects on glucose control, and additional intensive glucose-lowering interventions do not confer clinical benefits compared to conservative approaches.

Preoperative Use of Incretins Is Associated With Increased Diabetes Remission After RYGB Surgery Among Patients Taking Insulin



GC Wood, Ann Surg 2015

5129-x

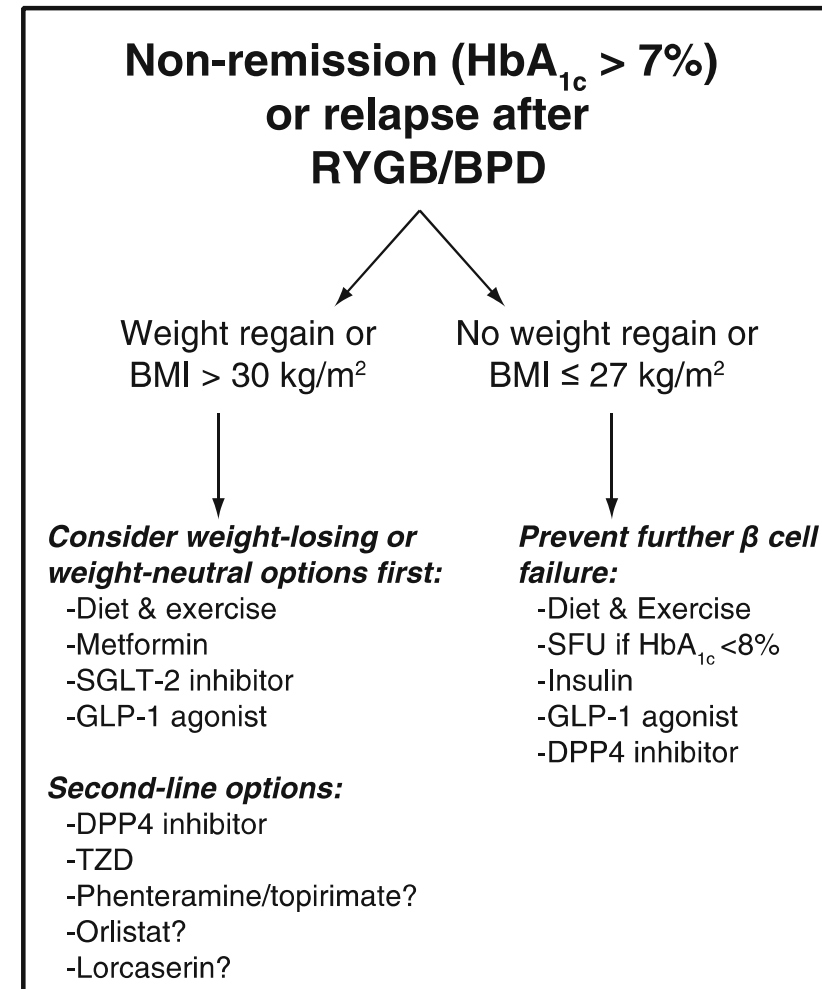
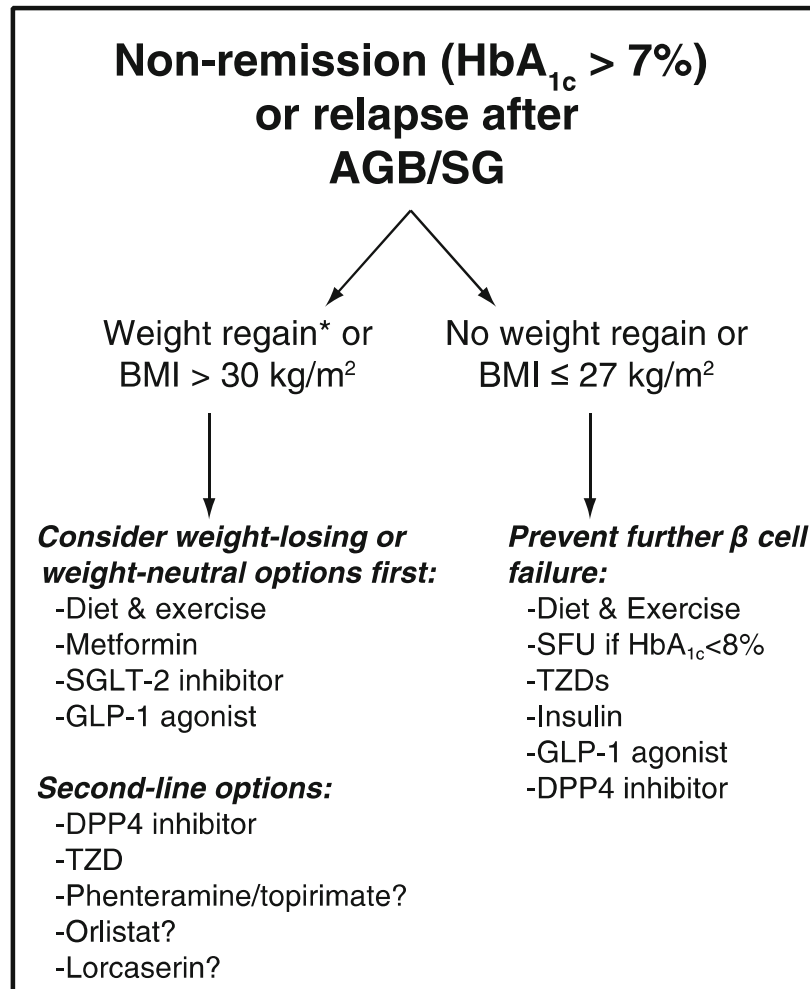
Jessica A. Zaman



Conclusion Bariatric surgery leads to significant resolution of type II diabetes and a prompt improvement in glucose tolerance in the perioperative period. Optimal glucose control as defined by the ASMBS was not associated with improved postoperative outcomes in our patient population but was highly predictive of long-term diabetes resolution.



LIPID AND METABOLIC EFFECTS OF GASTROINTESTINAL SURGERY (R COHEN, SECTION EDITOR)



Preoperative and Postoperative Recommendations			
Preoperative		Postoperative	
Oral	Insulin	Oral	Insulin
- Withdraw long-acting Sulfonylurea - Maintain or reduce glucose inhibitor, metformin, incretin, or DPP-4 inhibitor dose	- Decrease dose by about 50%^a - Nonhuman insulin is recommended ^c	- Reincorporate metformin (A1c <9%) - Add incretin, DPP-4, or glucose inhibitor (A1c >9%) - Subject to inquiry: introduce incretin analogue^d or glucose inhibitor as stand-alone therapy after discharge (A1c <9%)	- Decrease overall dose by about 50%^b - Human insulin is not recommended - Dose may have to be titrated down for up to 12 months - Premixed insulin may heighten hypoglycemic risk

Additional considerations and recommendations.

Preoperatively

1. Try to implement an exercise regimen with a very low calorie diet to offset decreases in lean muscle mass. Note that total caloric intake may need to be increased slightly as a result.
2. Maintain some communication with the patient to help reduce the incidence of hypoglycemia and to facilitate adherence.
3. If the patient is more poorly controlled, then they will likely necessitate a more intensive insulin regimen during the inpatient stay. Further, the implications for medication withdrawal and/or reincorporation, in the postoperative period, will be different than for those who are more optimally controlled. Thus, preparation can begin during the preoperative period.

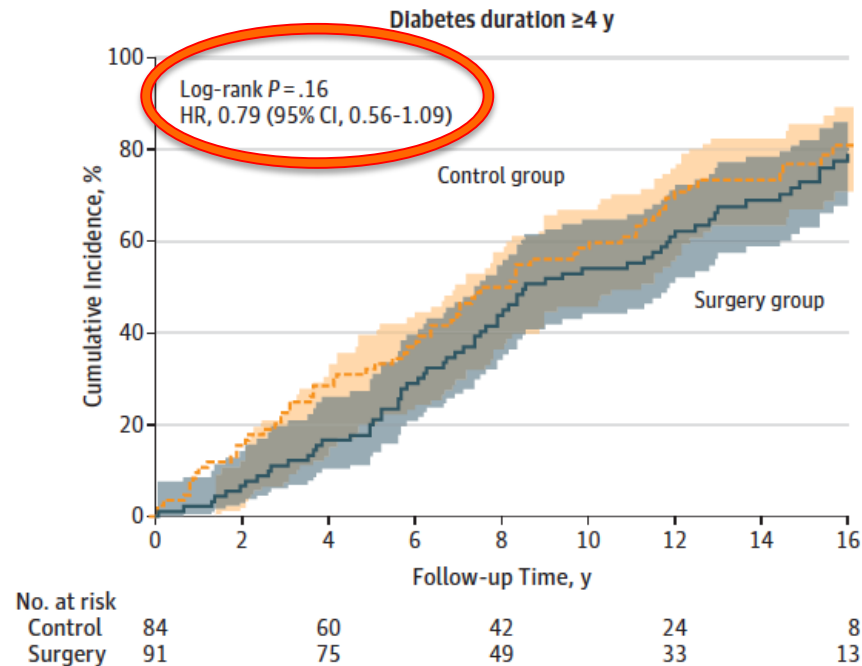
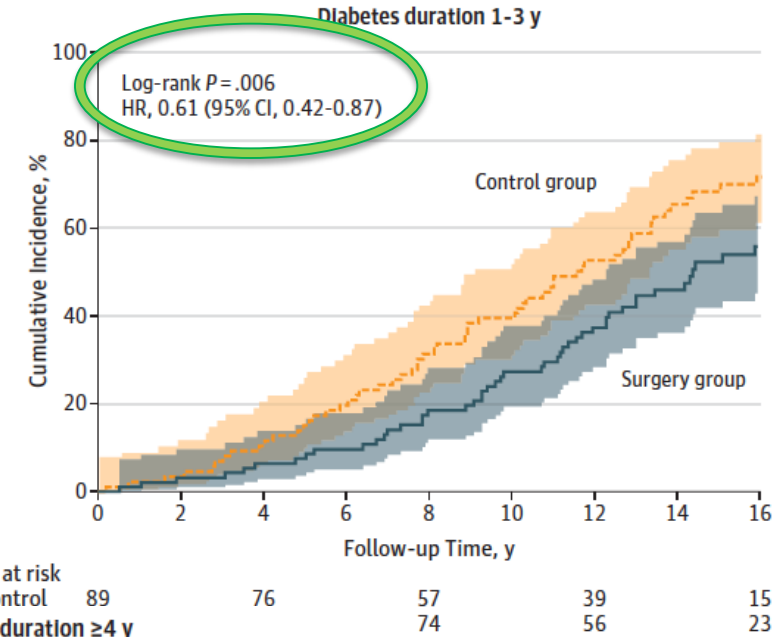
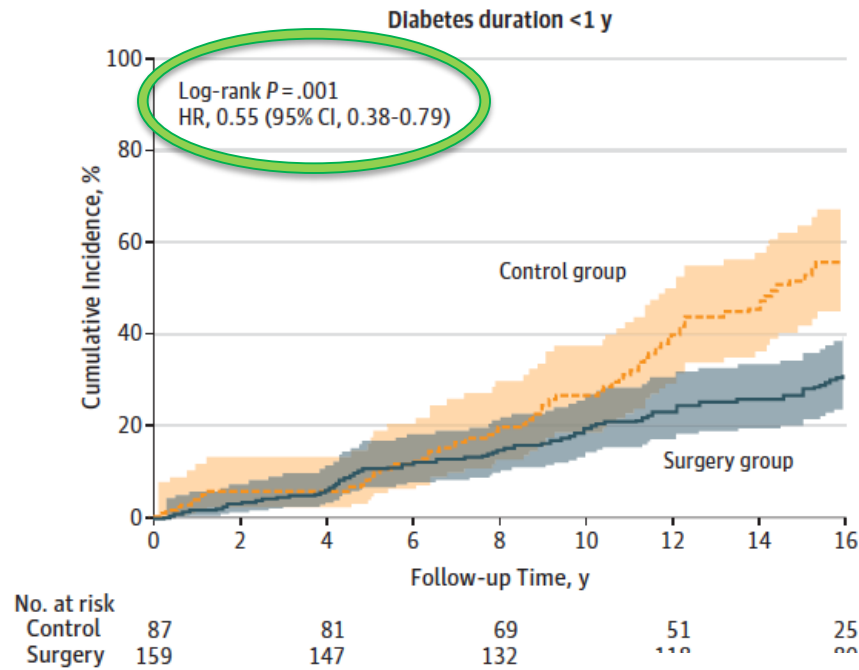
Perioperative and inpatient setting

1. Implement an insulin protocol that minimizes the risk of hypoglycemia and hyperglycemia.
2. Depending on the patient's state, a continuous infusion or rapid acting insulin regimen are recommended during perioperative period.¹⁸
3. Monitor blood glucose levels diligently.
4. Prepare for and refine patient-specific discharge guidelines.

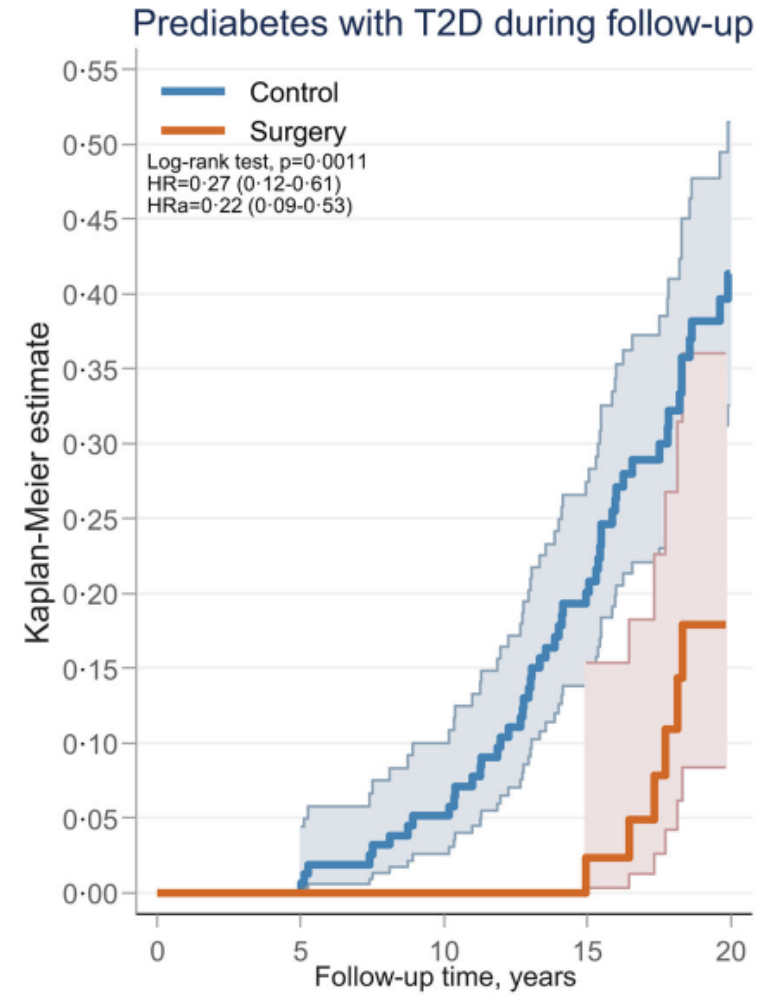
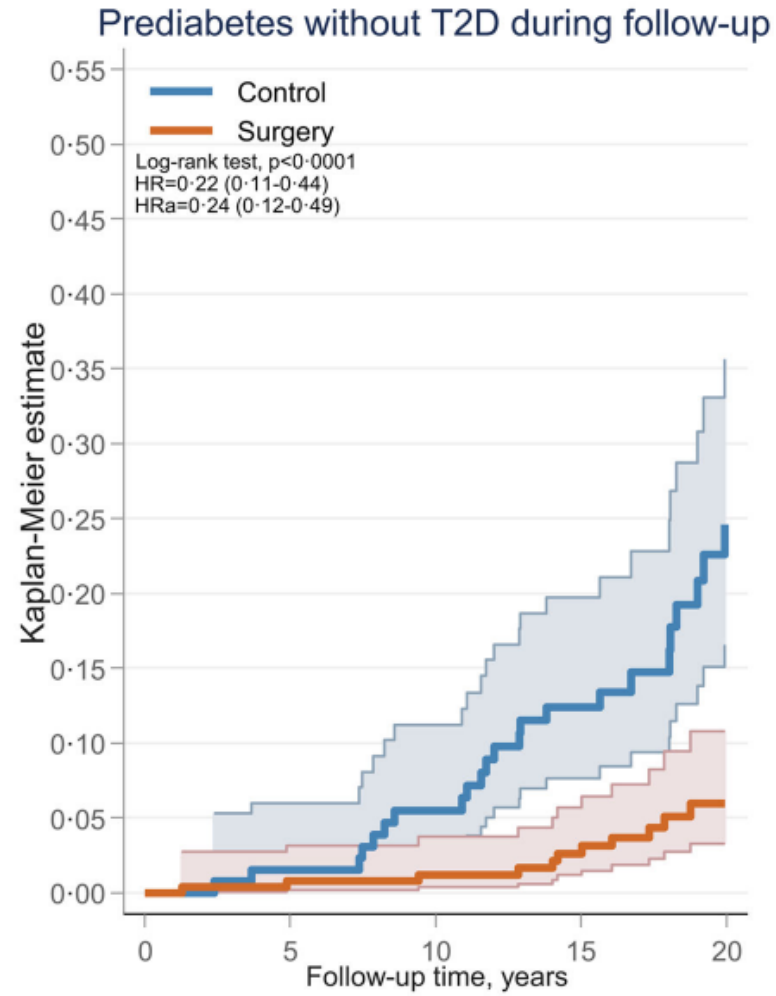
Postoperatively

1. Have the patient meet with a multidisciplinary team if possible. For instance, appropriate follow-up with the surgeon, endocrinologist, dietician, and if possible a trained fitness professional is recommended.
2. Exercise and dietary adherence is advised for more favorable and durable outcomes.

Cumulative Incidence of Micro e Macrovascular Complications



Cumulative incidence of microvascular events after bariatric surgery or usual care in subgroups stratified by glucose status



Diabetes: Bariatric surgery for T2DM--cure, or remission and relapse?



Medicine

Positives

- Conservative approach
- Multiple novel therapeutic options for diabetes and weight management
- Maintains integrity of the GI tract
- No surgical morbidity or mortality risks

Negatives

- Relies on adherence to lifestyle and medicine
- Difficult to achieve and sustain weight loss
- Progressive decline in beta cell function
- Long term safety of novel therapies uncertain

Bariatric Surgery

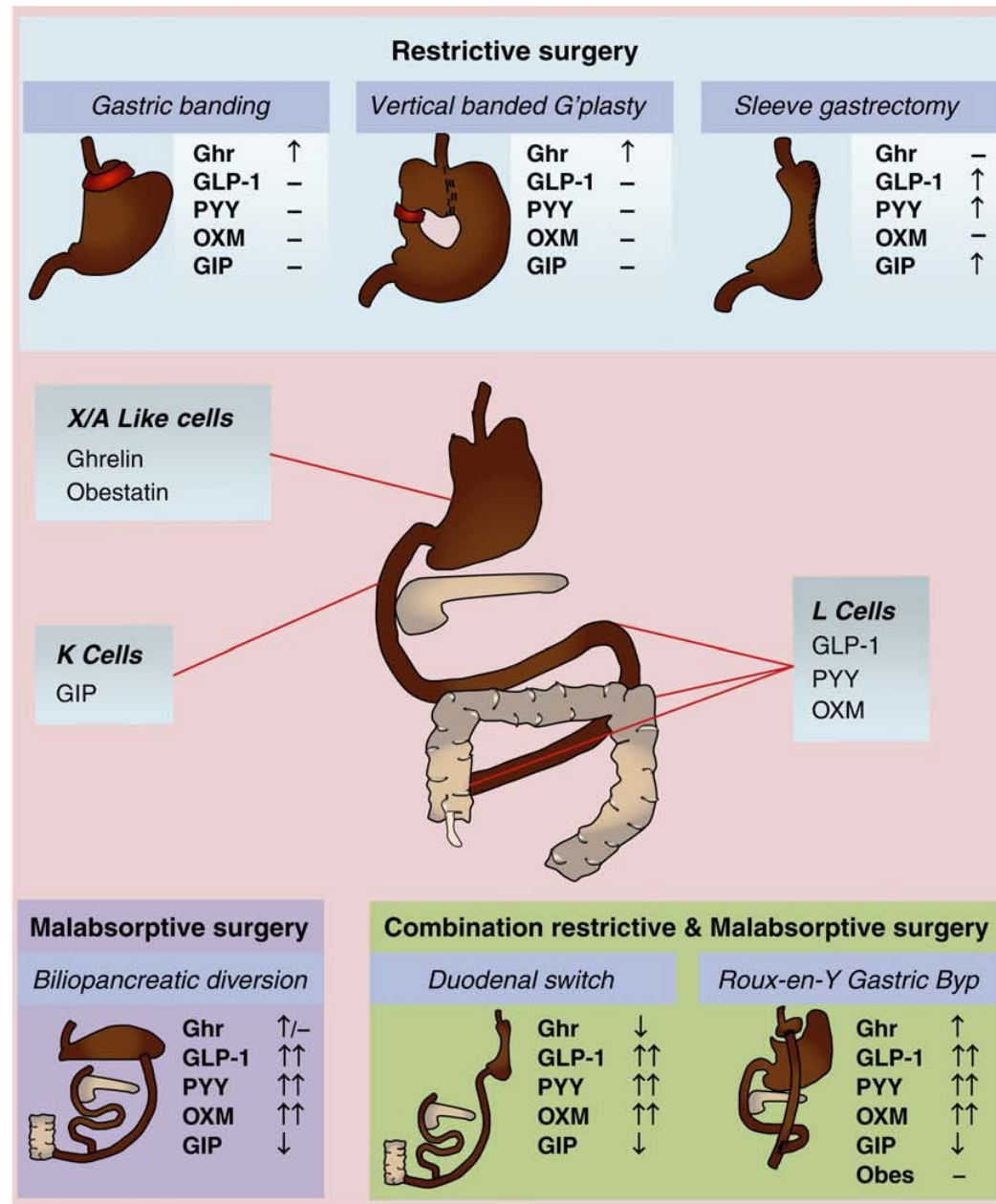
Positives

- Substantial & sustained weight loss for most
- Diabetes remission or improvement
- Reductions in weight-related conditions
- Reduced hospitalizations for diabetes complications affecting the eyes, kidneys, peripheral nerves, or peripheral circulation
- Improved long term survival possible

Negatives

- Lifelong nutritional management needed
- Weight regain
- Diabetes recurrence in some
- Short-term risk: bleeding, infection, thromboembolism, dehiscence, leaks, hernias, small bowel obstruction, cardiovascular events, rare procedure-related deaths
- Long-term complications: nutritional deficiencies, vomiting, gastritis, adhesions & strictures, gallstones, revisional surgery, dumping syndrome, hypoglycemia, depression

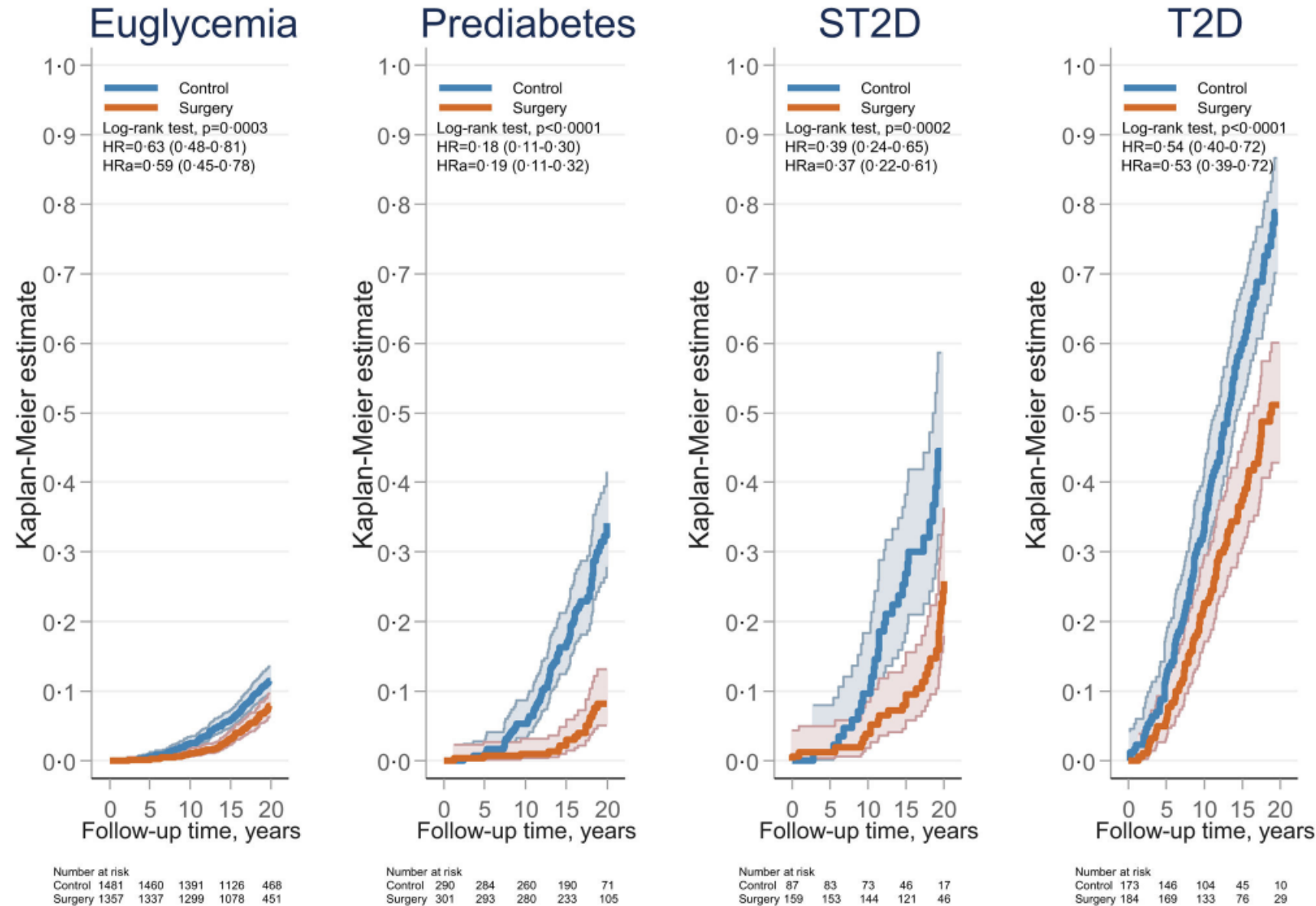
Emerging therapies in the treatment of 'diabesity': beyond GLP-1



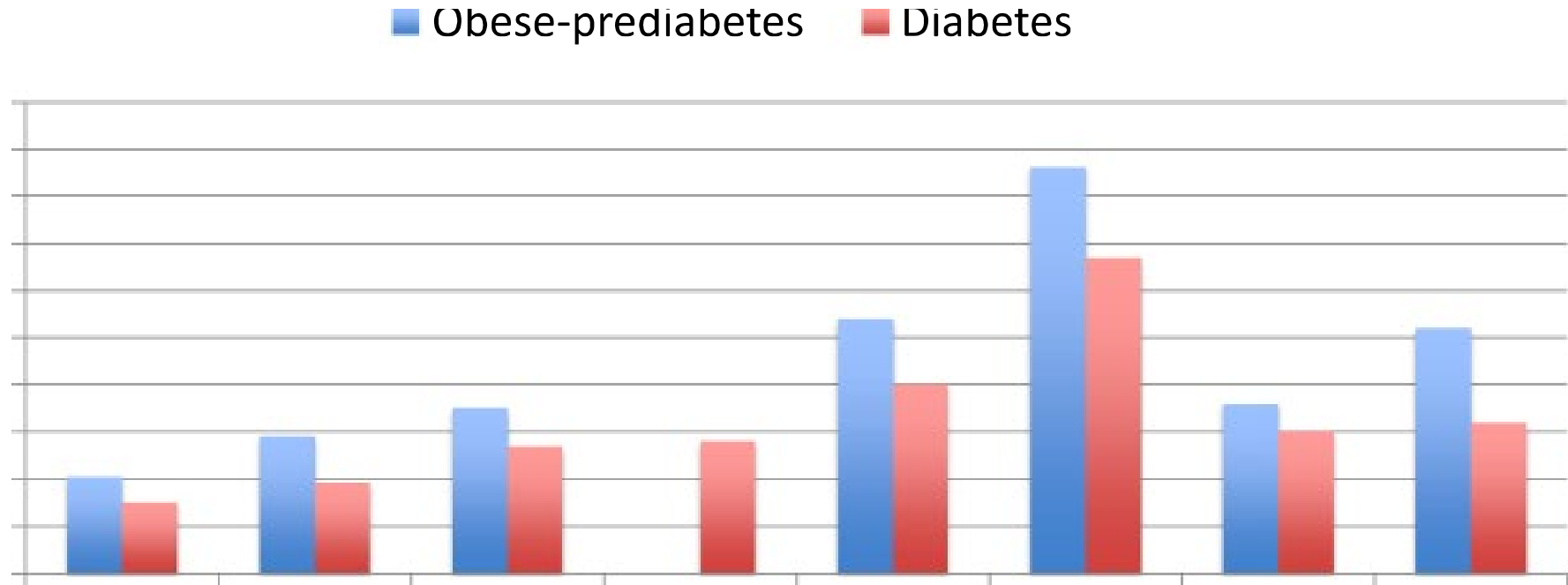
Randomized controlled trials that evaluated the effect of upper gastrointestinal bypass surgery in inducing remission of type 2 diabetes

Author	Follow-up	Intervention	Weight loss (%)	Remission criteria	Remission (%)
Ikramuddin <i>et al.</i> 2013 [5]	1 year	RYGB: <i>n</i> = 60 MLT: <i>n</i> = 60	RYGB: 26. MLT: 7.9	HbA1c ≤6.0%	RYGB: 44 MLT: 9
Courcoulas <i>et al.</i> 2014 [6]	1 year	RYGB: <i>n</i> = 20 LAGB: <i>n</i> = 21 MLT: <i>n</i> = 20	RYGB: 27.0 LAGB: 17.3 MLT: 10.2	HbA1c <6.5% FPG <126 mg/dL No T2D medication	RYGB: 50 LAGB: 27 MLT: 0
Schauer <i>et al.</i> 2012 [7]	1 year	RYGB: <i>n</i> = 50 SG: <i>n</i> = 50 MLT: <i>n</i> = 50	RYGB: 27.5 SG: 25.0 MLT: 5.2	HbA1c ≤6.0% No T2D medication	RYGB: 42 SG: 27 MLT: 0
Halperin <i>et al.</i> 2014 [8]	1 year	RYGB: <i>n</i> = 19 MLT: <i>n</i> = 19	BMI decrease ^a : RYGB: ~9.5 kg/m ² MLT: ~2.2 kg/m ²	HbA1c <6% FPG <100 mg/dL	RYGB: 32 MLT: 0
Schauer <i>et al.</i> 2014 [3]	3 years	RYGB: <i>n</i> = 48 SG: <i>n</i> = 49 MLT: <i>n</i> = 40	RYGB: 24.5 SG: 21.1 MLT: 4.2	HbA1c ≤6.0% No T2D medication	RYGB: 35 SG: 20 MLT: 0
Kehagias <i>et al.</i> 2011 [132]	3 years	RYGB: <i>n</i> = 30, T2D: <i>n</i> = 5 SG: <i>n</i> = 30, T2D <i>n</i> = 5	EWL ^a : RYGB: 62 SG: 68	FPG <126 mg/dL 2-h OGTT <200 mg/dL No T2D medication	RYGB: 80 SG: 80
Risstad <i>et al.</i> 2015 [133]	5 years	RYGB: <i>n</i> = 31, T2D <i>n</i> = 5 BPD-DS: <i>n</i> = 29, T2D <i>n</i> = 5	RYGB: 25.6 BPD-DS: 40.6	FPG <100 mg/dL No T2D medication	RYGB: 80 BPD-DS: 100
Mingrone <i>et al.</i> 2015 [4]	5 years	RYGB: <i>n</i> = 20 BPD: <i>n</i> = 20 MLT: <i>n</i> = 20	RYGB: 28.4 BPD: 31.1 MLT: 7.0	HbA1c <6.5% FPG <100 mg/dL No T2D medication	RYGB: 37 BPD: 63 MLT: 0

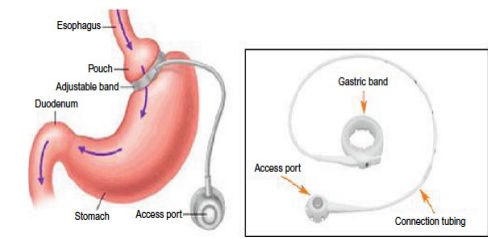
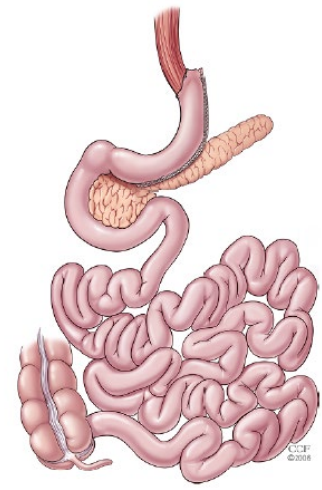
Cumulative incidence of microvascular events after bariatric surgery or usual care in patients with baseline prediabetes stratified by development of type 2 diabetes at or before the 15-year follow-up



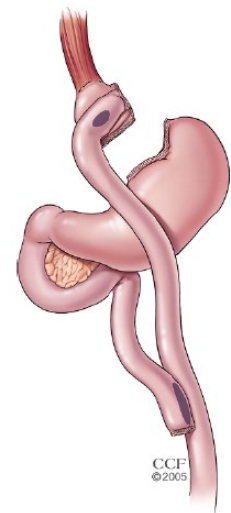
Weight loss of glucose-lowering and antiobesity drugs in obese people with prediabetes or type 2 diabetes.



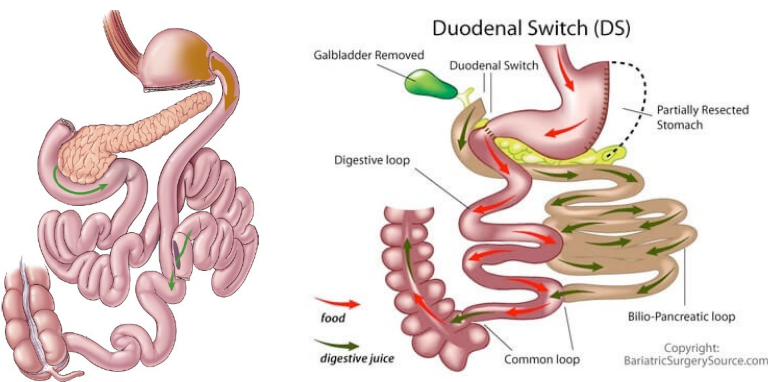
Gastrectomia Verticale (Sleeve Gastrectomy)



Bypass Gastrico (RYGB)

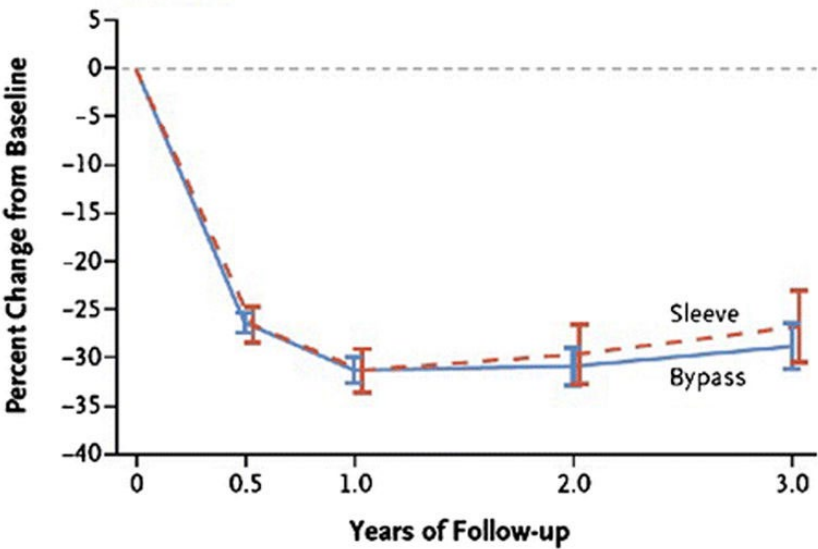


Diversione Biliopancreatica



Bariatric Surgery for Adolescents with Type 2 Diabetes: An Emerging Therapeutic Strategy

Weight Change from Baseline



No. of Participants

Bypass	161	140	140	137	131
Sleeve	67	56	61	58	52

3-year follow-up (Teen-LABS study)

	Baseline prevalence of condition [†] -- % (95% CI)	3-year follow-up prevalence of remission [†] -- % (95% CI)
Type 2 diabetes[*]		
Total	13 (8–20)	90 (65–98)
Gastric bypass	14 (9–23)	94 (66–99)
Sleeve gastrectomy	9 (3–22)	68 (7–99)
Prediabetes[‡]		
Total	10 (6–17)	77 (48–92)
Gastric bypass	13 (7–22)	94 (66–99)
Sleeve gastrectomy	∫	∫
Dyslipidemia^β		
Total	76 (69–81)	66 (56–74)
Gastric bypass	79 (71–85)	70 (59–79)
Sleeve gastrectomy	69 (55–80)	55 (36–73)
Elevated blood pressure^α		
Total	43 (35–51)	73 (60–83)
Gastric bypass	46 (37–55)	78 (64–88)
Sleeve gastrectomy	35 (23–50)	53 (27–78)
Abnormal kidney function^ψ		
Total	17 (12–23)	86 (63–90)
Gastric bypass	19 (13–27)	84 (59–95)
Sleeve gastrectomy	12 (6–24)	∫

5–12 year follow-up (FABS-5+ study; RYGB only)

	Baseline	Long-term follow-up		
	Prevalence of condition [†] -- % (95% CI)	Prevalence of condition [†] -- % (95% CI)	Prevalence of remission (observed)	Incidence (observed)
Diabetes[*]	16.1 (8.5–28.3)	1.8 (0.2–12.0)	7/8 (88%)	0/45 (0%)
Dyslipidemia^β	85.7 (73.8–92.8)	38.2 (26.3–51.7)	29/45 (64%)	4/8 (50.0%)
Elevated blood pressure^α	47.4 (34.7–60.4)	16.4 (8.4–28.7)	19/25 (76%)	3/29 (10.3%)

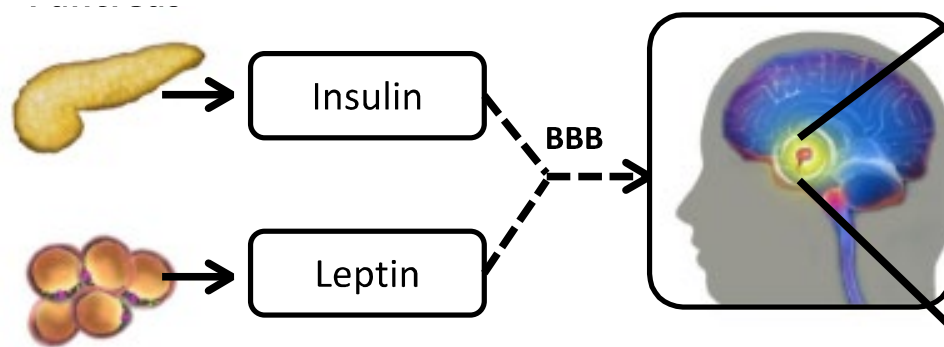
Some of these issues are summarized below:

- Long-term (beyond 10 years) efficacy and safety data are lacking.
- Factors predicting T2DM remission and relapse after surgery are still incompletely characterized.
- There is still insufficient evidence to clearly define cut-off values for T2DM duration or laboratory markers that might be able to quantitatively predict T2DM remission over time.
- Available studies include a modest number of patients with a BMI between 30 and 35 kg/m². There are limited comparative (head-to-head) data for distinct surgical interventions in terms of cardiometabolic outcomes.
- Data for T2DM-related complications, cancer and mortality, representing hard and clinically relevant endpoints, can be extrapolated only from non-randomized studies. RCTs for these outcomes are warranted.
- There are no studies investigating the role of multimodal therapy with integration of pharmaceutical and surgical treatment strategies to optimize outcomes for T2DM patients, in terms of inducing and maintaining T2DM remission as well as lowering the risk of complications and comorbidities.
- It is necessary to identify more reliable clinical and biological markers, which can be applied in an accurate definition of T2DM remission and cure.
- Cost-effectiveness data are pending.
- Optimal intervention time for a durable T2DM remission still remains elusive.
- The relationship between the duration of T2DM remission and the incidence of micro- and macrovascular complications remains unclear.

Effects of glucose lowering and antiobesity drugs on weight loss in obese people with and without type 2 diabetes

	Placebo-subtracted weight loss and changes in glycemic parameters		
	Overweight/obese	Prediabetes	Type 2 diabetes
Metformin 850 mg BID	1%	DPP/DPPOS (19), 10 years 1.9 kg (2%) 18% ↓ diabetes risk 2-year delay in onset of diabetes	Meta-analysis 31 trials BMI 5.3% ↓
GLP-1 RAs			
Liraglutide 1.8 mg QD	N = 564, 20 weeks 2.7 kg		LEAD-6 (29), 26 weeks N = 233 3.24 kg A1C ↓ 1.12%
Exenatide 10 µg BID			LEAD-6 (29), 26 week N = 231 2.87 kg A1C ↓ 0.79%
SGLT2 inhibitors			
Canagliflozin 100 mg			(46–48) 2.3 kg; A1C ↓ 0.9%
300 mg			3.3 kg; A1C ↓ 1%
Dapagliflozin 5 mg			(46,48) 1.8 kg, A1C ↓ 0.5%
10 mg			2.4 kg, A1C ↓ 0.7%
Empagliflozin 10 mg QD			(48,49) 2.3 kg, A1C ↓ 0.5%
25 mg QD			2.5 kg, A1C ↓ 0.6%
Orlistat	2.9 kg (~3%)	XENDOS (33), 4 years N = 3305 Baseline wt 110.5 kg 2.8 kg 37% ↓ diabetes risk	1 year (50) N = 391 Baseline wt 100 kg 1.9% A1C ↓ 0.46%
Liraglutide	SCALE Prediabetes/obesity without diabetes (36), 56 weeks N = 3731 Baseline wt. 106 kg 5.6 kg (5.4%)	SCALE Prediabetes/obesity without diabetes (36), 56 weeks N = 3731, 2283 with prediabetes Baseline wt. 106 kg 5.6 kg (5.4%) Progression to diabetes 4 (lira 3.0 mg) 14 (placebo) 71% diabetes risk reduction Reversion to normoglycemia 69% (lira 3.0 mg) 33% (placebo)	SCALE diabetes (37), 56 weeks N = 846 Baseline wt. 106 kg At 56 weeks 2.7% (lira 1.8 mg) 4.0% (lira 3.0 mg) A1C↓ 0.74% (lira 1.8 mg) 0.93% (lira 3.0 mg)
Phentermine-topiramate PHEN/TPM CR 7.5/46 mg 15/92 mg	CONQUER (51), 56 weeks N = 2487 Baseline wt 103 kg 6.7 kg (6.6%) (7.5/46 mg) 8.8 kg (8.6%) (15/92 mg)	SEQUEL (52), 52 + 56 week ext N = 475, prediabetes or MetSyn Baseline wt 103 kg 8.4% (7.5/46 mg) 9.6% (15/92 mg) Progression to diabetes 6.1% (placebo) 1.8% (7.5/46 mg) 1.3% (15/92 mg) Diabetes risk reduction 49% (7.5/46 mg) 89% (15/92 mg)	OB-202/DM-230(40), 56 weeks N = 130 Baseline wt 94.9 kg 6.7% A1C↓ 0.4% CONQUER (40,51), 56 weeks N = 388 Baseline wt103 kg 8.1 to 10.2 kg A1C↓ 0.1%
Phentermine	3.6 kg		

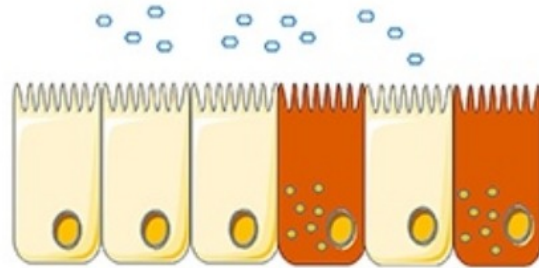
Central regulation of appetite. The hypothalamus controls appetite by integrating peripheral humoral signals that influence food intake and energy expenditure by means of neural signals from the brain stem and higher cortical centres.



Intestinal adaptation to bariatric surgery

Positive impact of intestinal adaptation

Pharmacological mimicry

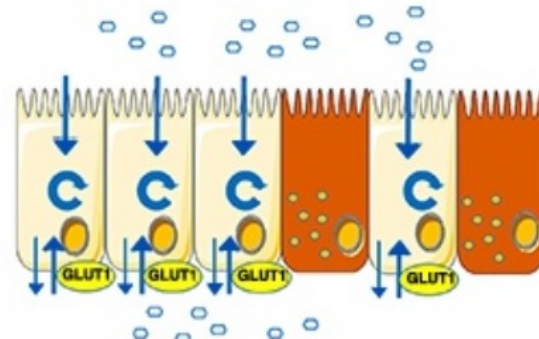


Increased number of GLP-1+ cells
Increased sensitivity of GLP-1+ cells ?

Increased
GLP1 secretion

GLP-1 R agonists
DPP-IV inhibitors

Decrease alimentary glucose transport



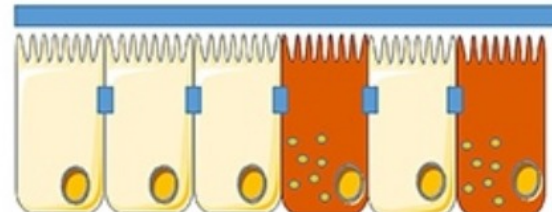
*Increase blood glucose consumption
(after RYGB)*

Prevention of
hyperglycemic excursion

Acarbose

Reduction of glycemia

Metformin

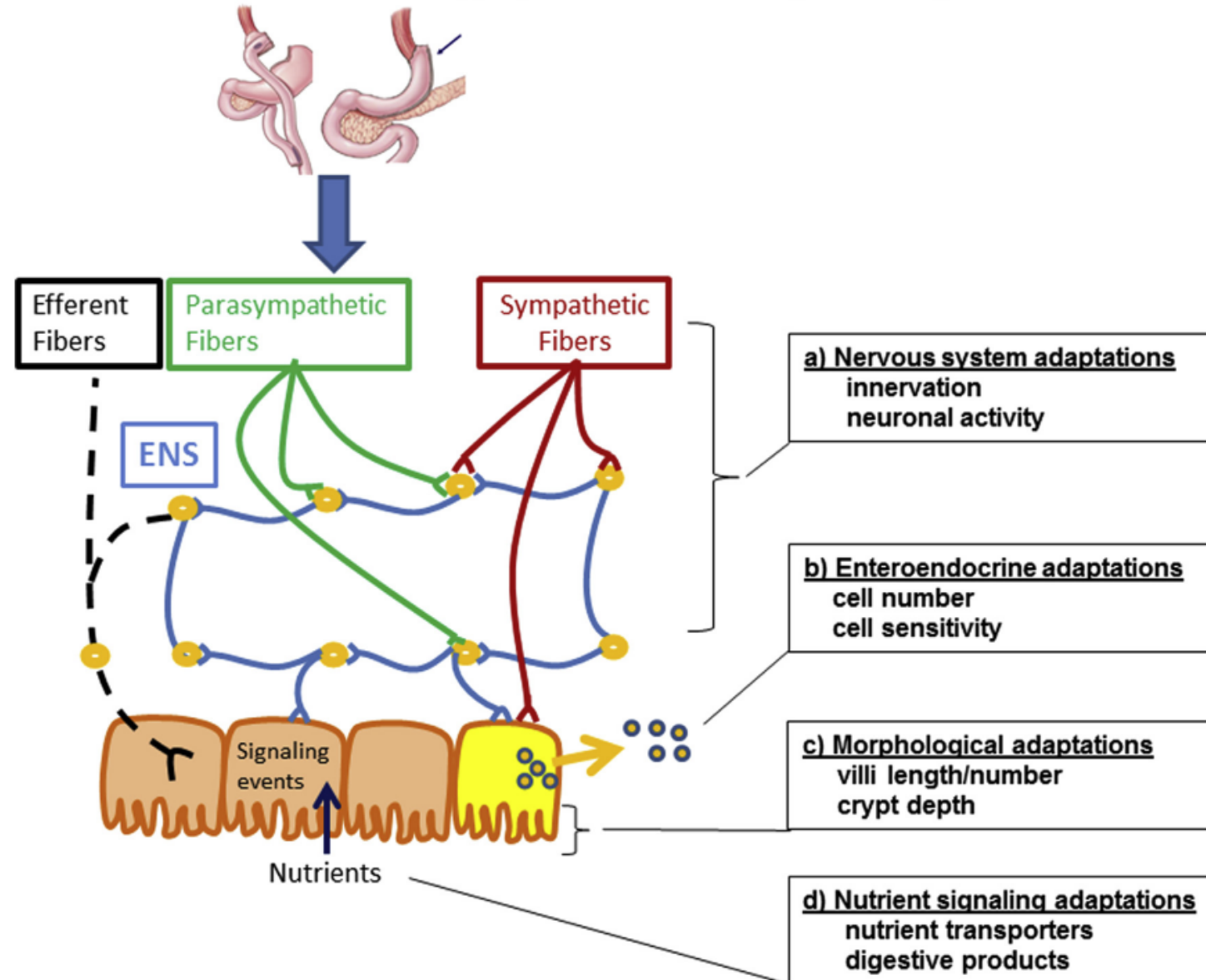


Increased expression of junction protein ?
Thicker mucus layer ?
Changes in mucus composition ?

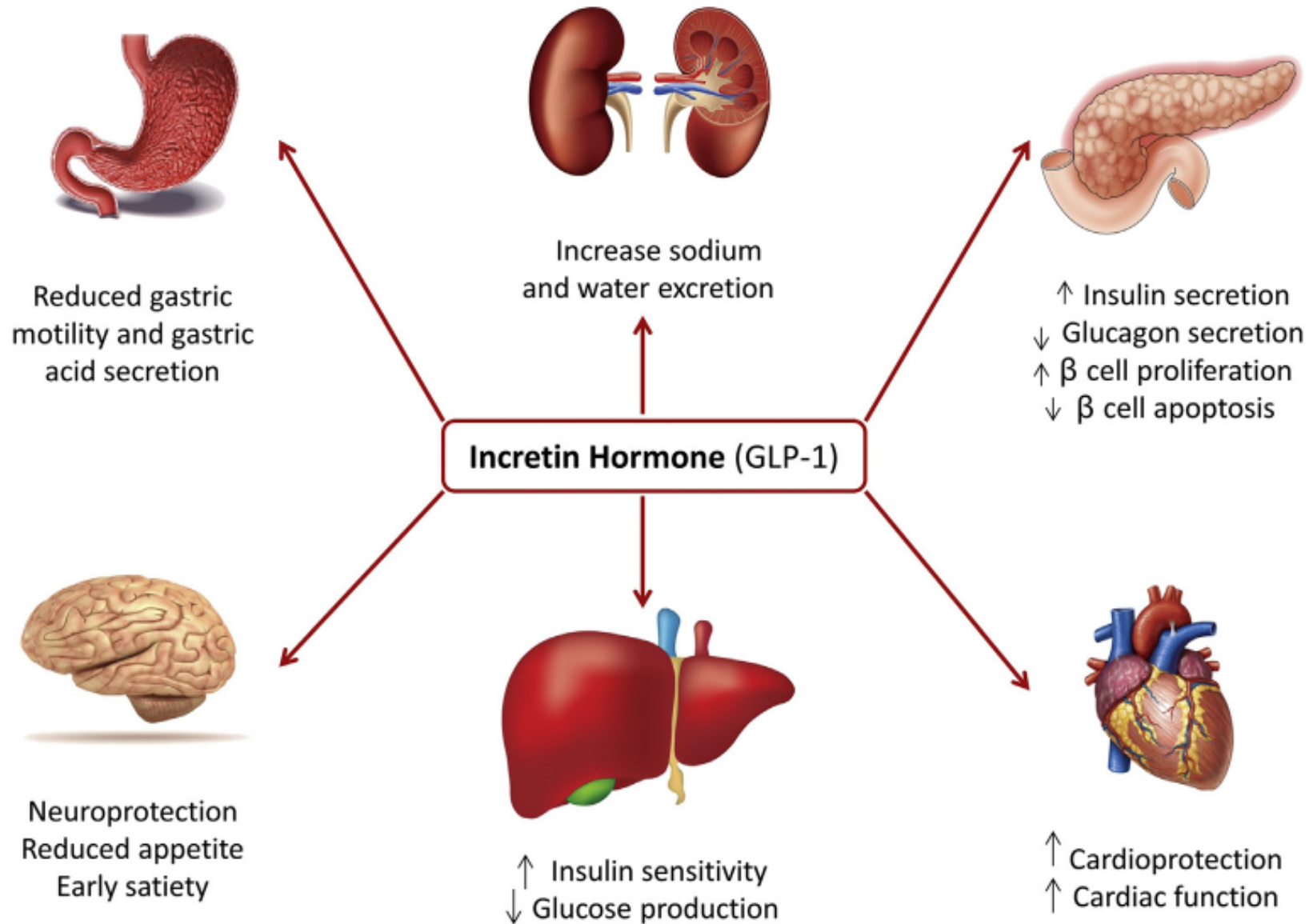
Ameliorated
barrier function ?

Akkermansia muciniphila
GLP-2

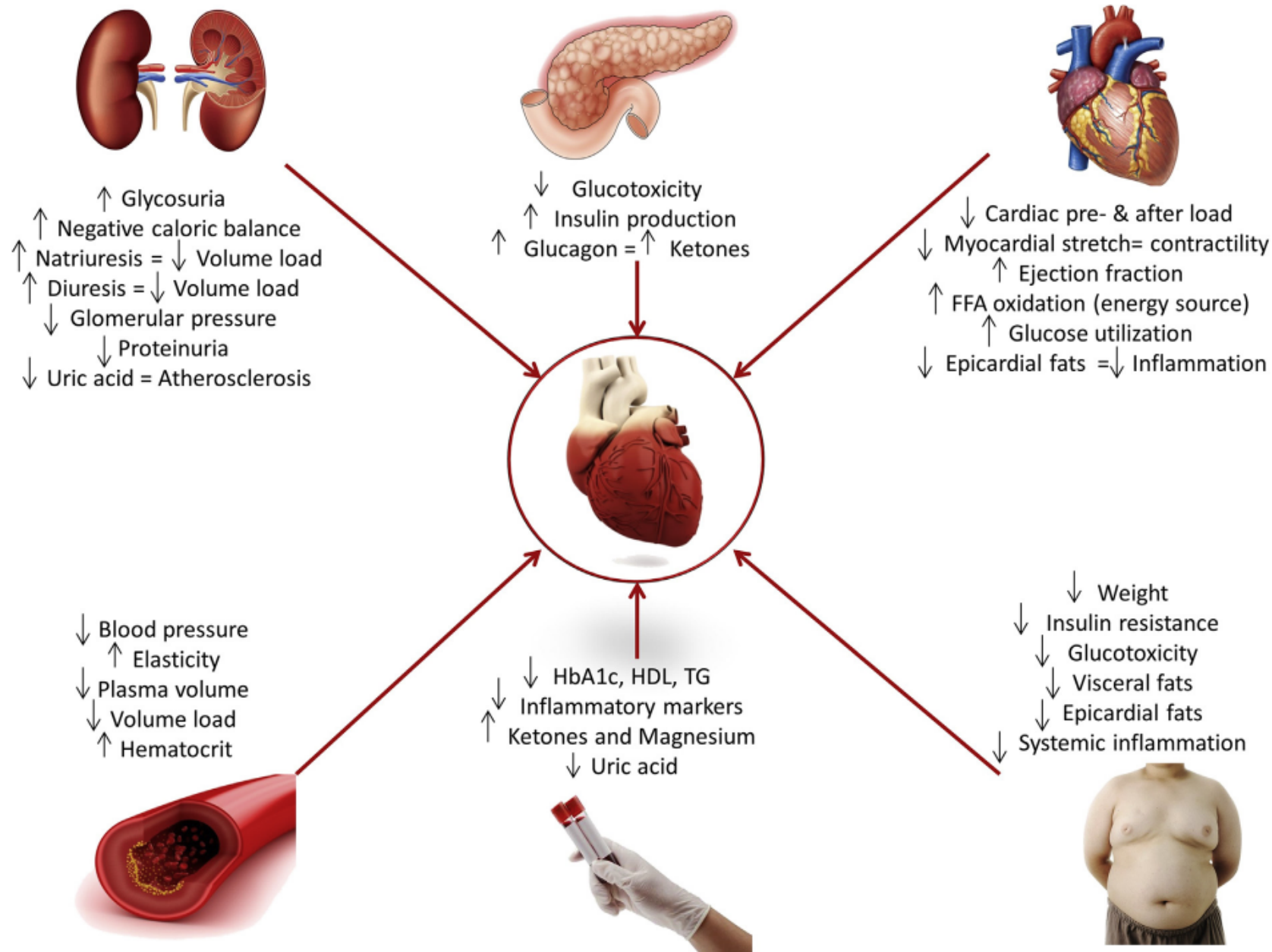
Bariatric surgery-driven enteroplasticity



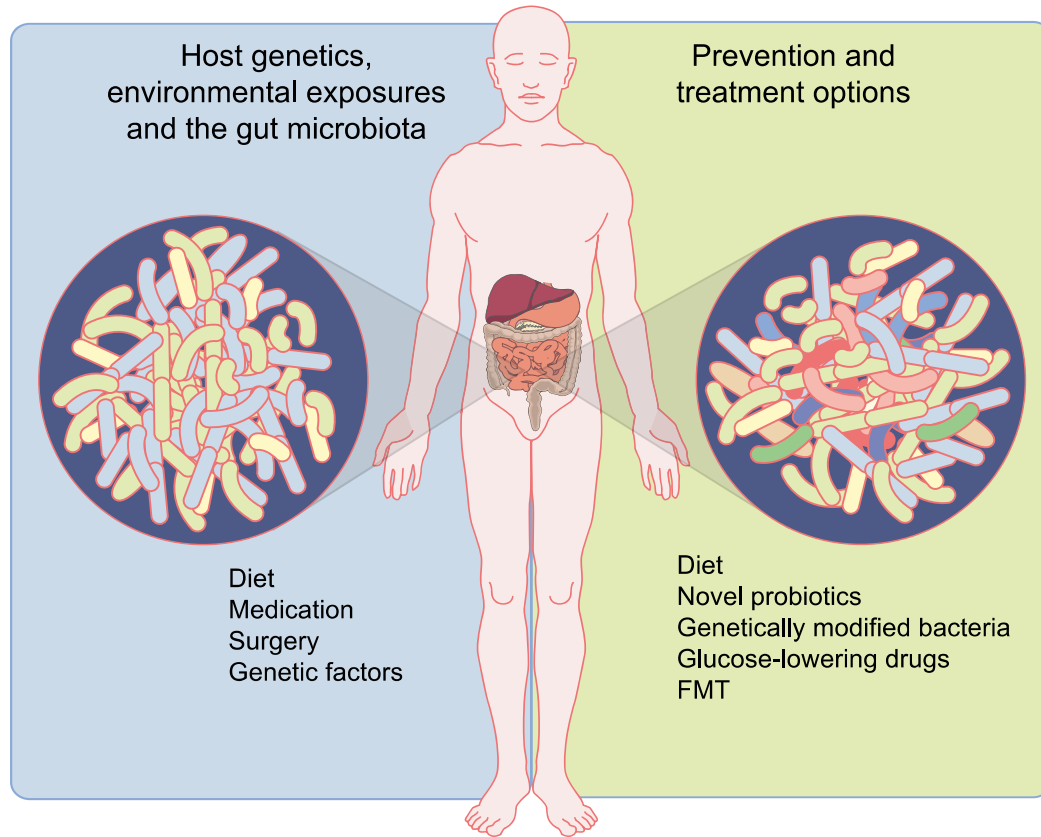
The physiological roles of glucagon like peptide-1 and the potential therapeutic benefits of glucagon like peptide-1 receptor (GLP-1RA) manipulation.



The putative mechanisms of cardiovascular protection conferred by sodium glucose cotransporter-2 (SGLT-2) inhibitor therapy.



The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities



Current human evidence

Dysbiotic microbiota

Slightly altered overall bacterial composition

↓ Butyrate-producing bacteria

↓ *A. muciniphila*

↑ Serum BCAAs via *P. copri* and *B. vulgatus*

Glucose-lowering medication

↑ *Lactobacillus* and *Escherichia* species with metformin

Diet

↑ *Prevotella* with high-fibre diet in some individuals

Gut microbial composition may be used to identify responders to dietary interventions

Bariatric surgery

Effects on bacterial composition may play a role in the BMI-independent effects of surgery on glucose metabolism

Future possibilities and challenges

Personalised nutrition and probiotic use

Synergistic approach: diet, probiotics and microbiota

Need for further studies of: (1) impact of habitual dietary intake on response; (2) single vs multiple probiotic strain effects; (3) use as an adjunct to glucose-lowering drugs

Targeted colonic delivery of SCFAs

No need for high intake of indigestible fibres/responsive gut microbiota

Targeted delivery of propionate decreases energy intake and improves glucose metabolism

Pasteurised probiotics

Enables production of probiotics of oxygen-sensitive anaerobic bacteria

Pasteurised *A. muciniphila* improves glucose metabolism in mice: human studies needed

Genetically modified bacteria

Recombinant bacteria can express therapeutic factors in microbiota

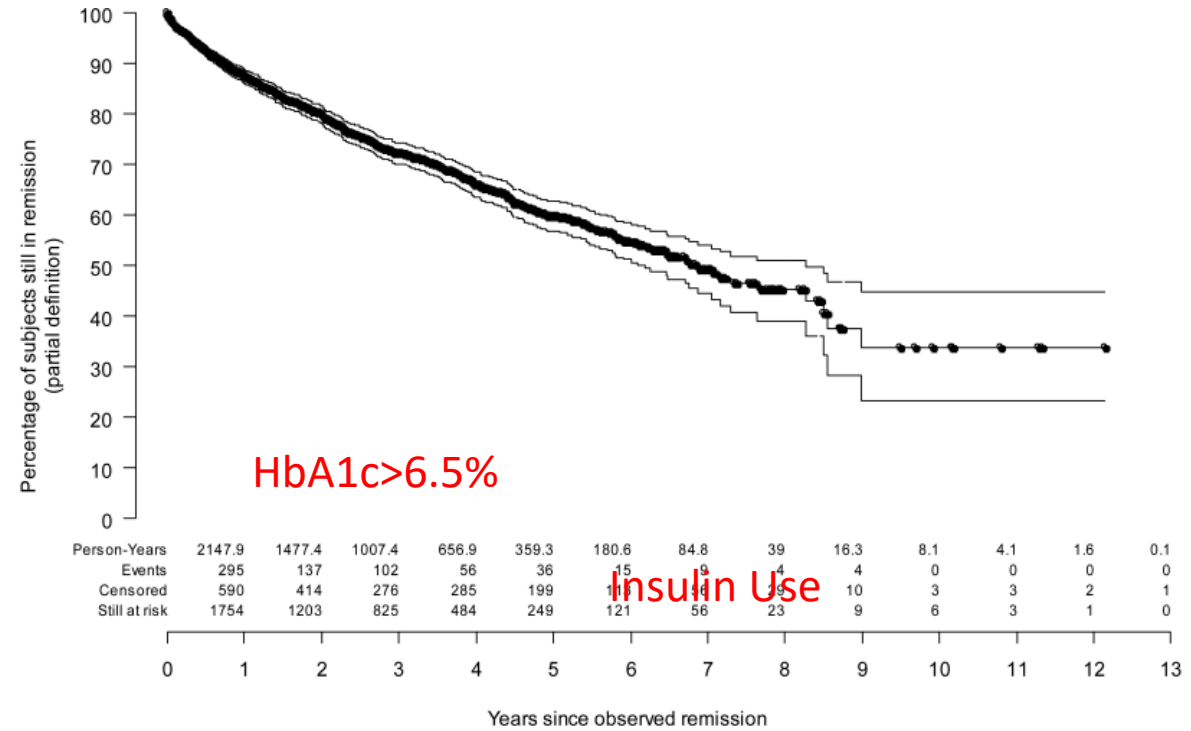
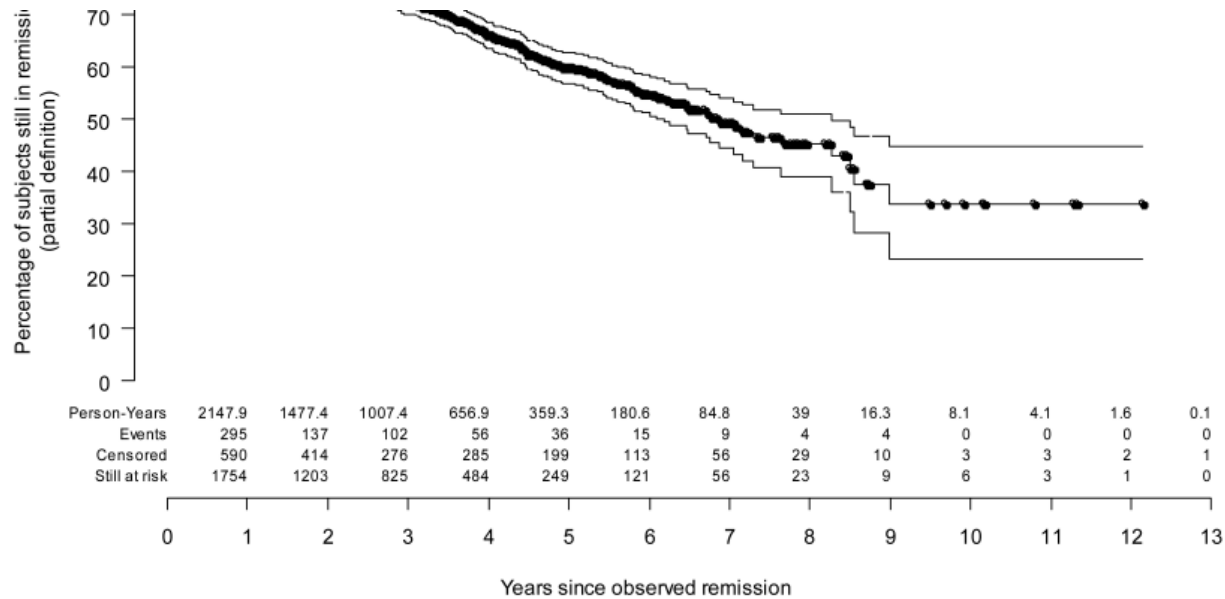
L. lactis modified to produce GLP-1, leading to improved glucose metabolism in mice: human studies needed

FMT

Little evidence for improved glycaemic control

Can potential risks be eliminated?

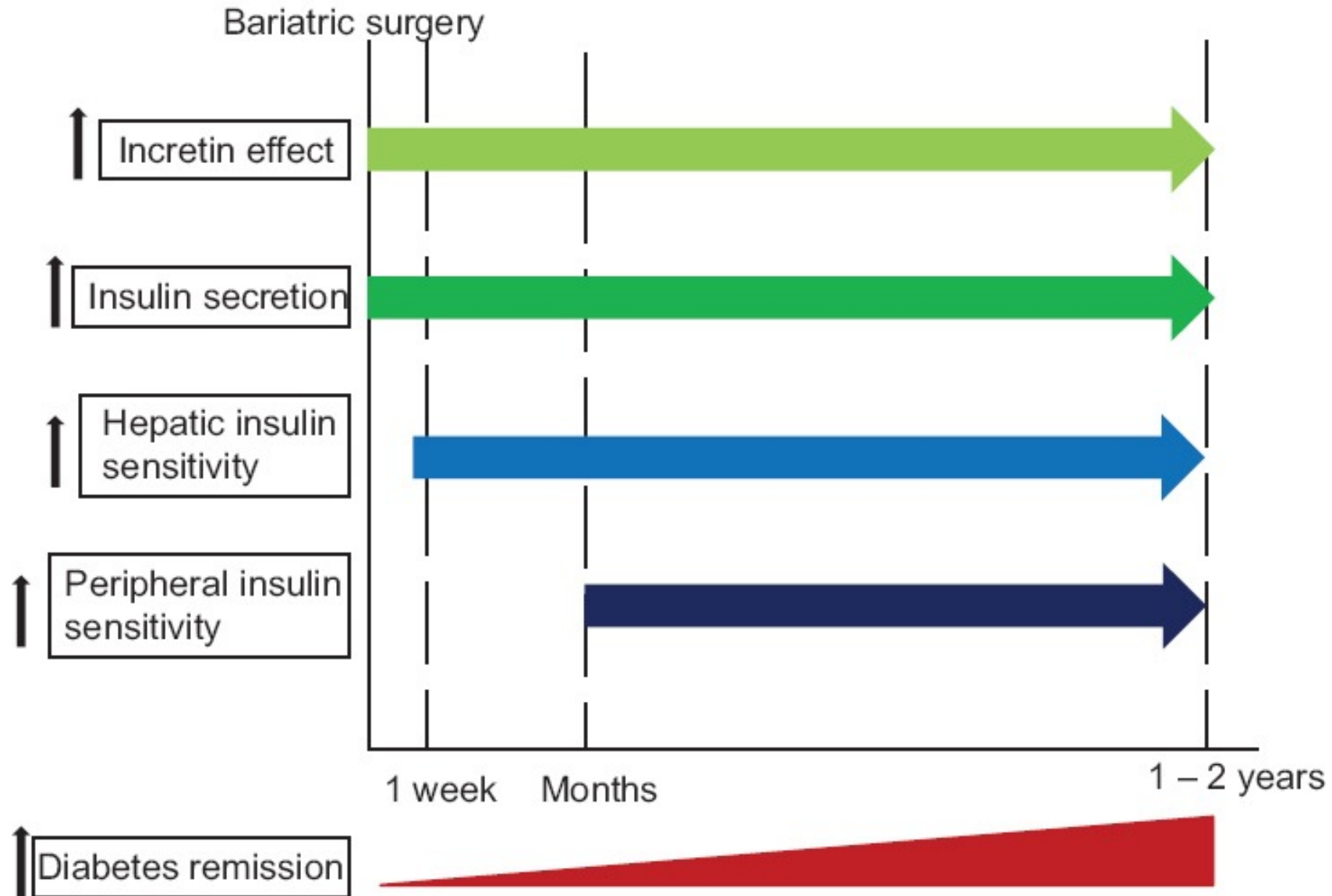
A Multisite Study of Long-term Remission and Relapse of Type 2 Diabetes Mellitus following Gastric Bypass

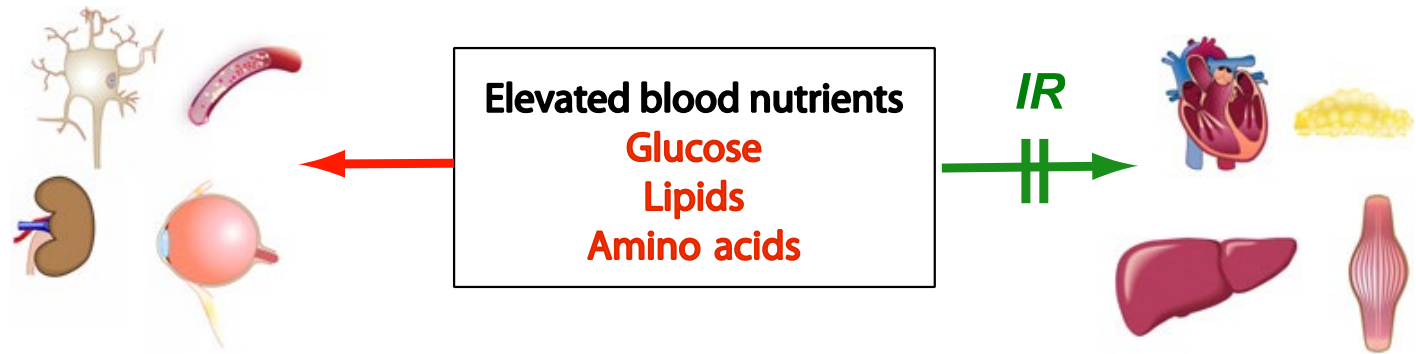


Randomized controlled clinical trials comparing T2D response to conventional medical versus surgical treatment in obese individuals.

Treatment group	Analysis N (per group)	Follow-up (years)	T2D remission rates (respective percentages)
Medical versus LAGB	30/30	2	13/73
Medical versus RYGB versus BPD	18/19/19	2	0/75/95
Medical versus RYGB versus SG	41/50/49	1	12/42/37
Medical versus RYGB versus SG	17/18/19	2	6.2/44.4/26.3
Medical versus RYGB	34/31	1	0/90
Medical versus RYGB	60/60	1	32/75

Proposed mechanism of diabetes remission





The role of bariatric surgery to treat diabetes: current challenges and perspectives

Reference	Study population	Intervention	Duration of follow-up	Major outcomes	Key results
Sjöström et al., 2004 [35]	SOS cohort	LAGB, VBG, RYGB	10 years	CVD risk factors (remission/prevention)	↑ recovery from T2DM, dyslipidemia, HTN and hyperuricemia, ↓ incidence of T2DM and lipid disorders after surgery
Adams et al., 2007 [49]	N = 9949	RYGB	7.1 years	Total and cause-specific mortality	↓ T2DM-, cancer- and CHD-related mortality, ↑ mortality related to accidents and suicide after RYGB
Sjöström et al., 2007 [48]	SOS cohort	LAGB, VBG, RYGB	10.9 years	Overall mortality	↓ CVD, cancer and overall mortality after surgery vs. usual conventional care
Iaconelli et al., 2011 [39]	N = 110, BMI > 35, newly diagnosed decompensated T2DM	BPD	10 years	Micro- and macrovascular complications, renal function, T2DM remission	↑ recovery from microalbuminuria, ↓ CHD probability after surgery vs. medical arm
Adams et al., 2012 [36]	N = 1156, BMI > 35	RYGB	6 years	Weight loss, T2DM remission	Superior weight loss maintenance, ↑ T2DM remission, ↓ T2DM incidence after surgery vs. control group
Sjöström et al., 2012 [45]	SOS cohort	LAGB, VBG, RYGB	14.7 years	Stroke, myocardial infarction	↓ CVD incidence and mortality after surgery vs. usual conventional care
Arterburn et al., 2013 [26]	N = 4434, inadequately controlled T2DM	RYGB	10 years	T2DM remission	68% T2DM remission within 5 years post-RYGB, 35% relapse within 5 years after initial remission, median duration of remission 8.3 years
Brethauer et al., 2013 [44]	N = 217	LAGB, RYGB, SG	6 years	T2DM remission, cardiometabolic comorbidities	25% T2DM remission after surgery, 19% T2DM relapse after initial remission, up to 80% control of cardiometabolic risk factors
Sjöström et al., 2014 [40]	SOS cohort	LAGB, VBG, RYGB	18 years	T2DM remission, micro- and macrovascular complications	↓ incidence of micro- and macrovascular T2DM-related complications
Arterburn et al., 2015 [47]	N = 2500, mainly ♂	LAGB, RYGB, SG	14 years	Mortality/ survival	↓ all-cause mortality after surgery
Mingrone et al., 2015 [8]	N = 60, BMI > 35, inadequately controlled T2DM for at least 5 years	RYGB, BPD	5 years	T2DM remission, CVD risk, medication use, QOL, diabetes-related complications	↑T2DM remission but existing risk of relapse, ↓ lipids, CVD risk, medication use and major complications after surgery vs. conventional diabetes treatment
Schauer et al., 2017 [38]	N = 150, BMI 27–43, poorly controlled T2DM	RYGB, SG	5 years	HbA1c <6% with or without medication	Metabolic endpoint met by 29% of RYGB, 23% of SG and 5% of IMT group, superior weight loss, better lipid profile, ↓ use of insulin, ↑ QOL after surgery

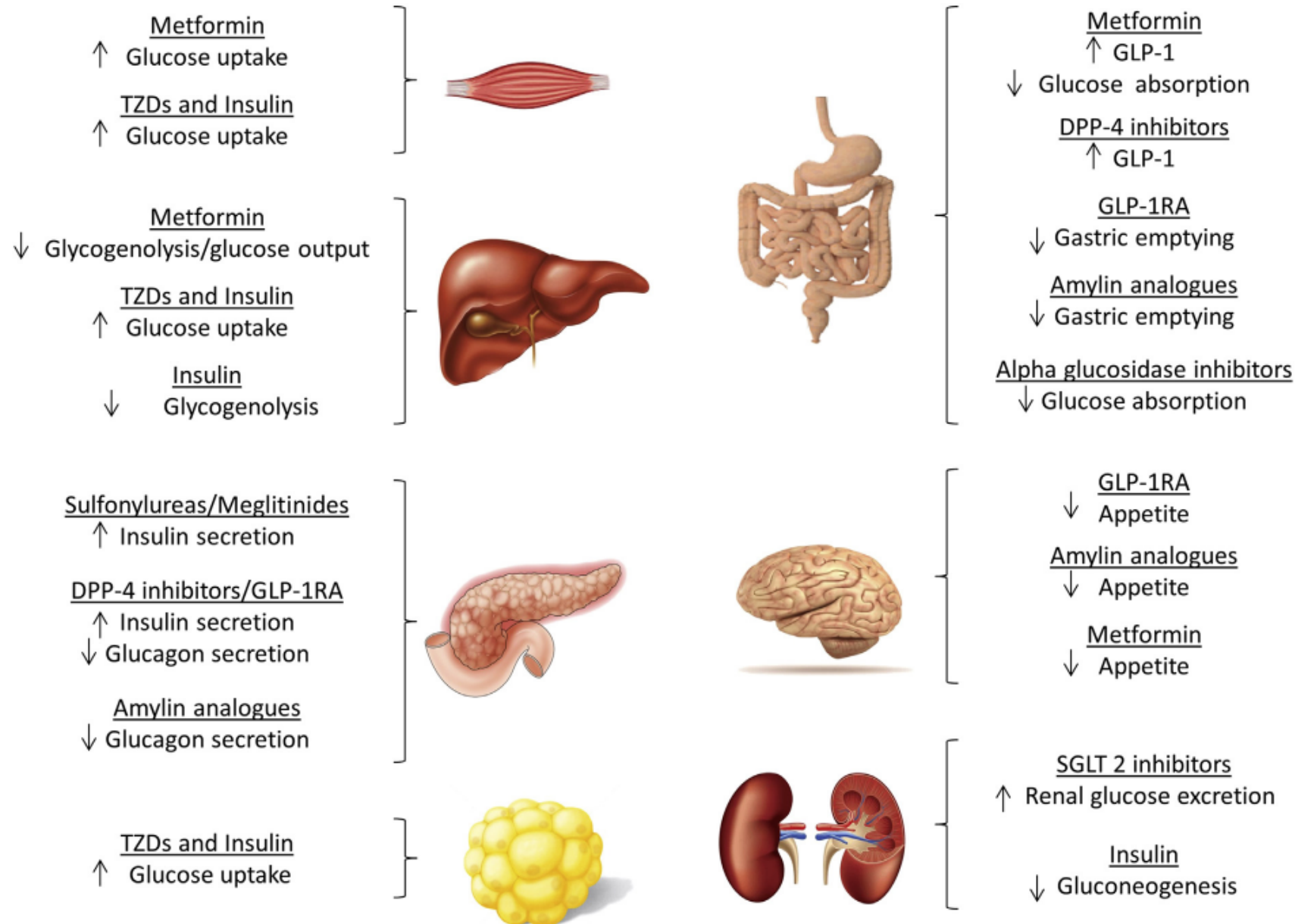
Diabetes Remission

Definition	Criteria
Improved diabetic control	• A significant reduction in A1C (by >11 mmol/mol or 1%) or • A significant reduction in fasting blood glucose (by >1.4 mmol/l or 25 mg/dL) or • A significant reduction in A1C and FBG accompanied by a decrease in antidiabetic medication requirement • At least 1year's duration
Partial remission	• Hyperglycemia below diagnostic thresholds for diabetes (HbA1c 42–47 mmol/mol; fasting glucose 100–125 mg/dL (5.5–6.9 mmol/l)) • At least 1 year's duration • No active pharmacologic therapy or ongoing procedures
Complete remission	• Normal glycemic measures (HbA1c <48 mmol/mol; fasting glucose <125 mg/dl (7.0 mmol/l)) • At least 1 year's duration • No active pharmacologic therapy or ongoing procedures
Prolonged remission	• Complete remission of at least 5 years' duration

The potential mechanisms of actions of individual antidiabetic drug classes mediated through different organs in the body on diabetes and diabetesity.



Pappachan JM, 2018



Summary of Recommendations for Adjustment of Antidiabetic Medication before and after Bariatric Surgery

During preoperative low calorie diet (approximately 2 weeks prior to surgery)

- Withdrawal of insulin secretagogues is recommended
- Reduce premix or rapid acting insulin by 50%
- Reduce NPH or long-acting analogs by 30%
- Monitor glucose at least twice a day
- Aim at plasma glucose 110–180 mg/dl. If glucose is repeatedly <90 mg/dl or hypoglycemia; further reduction of insulin (by 50%)