

Postprandiella Hypoglykemier post bariatrisk kirurgi

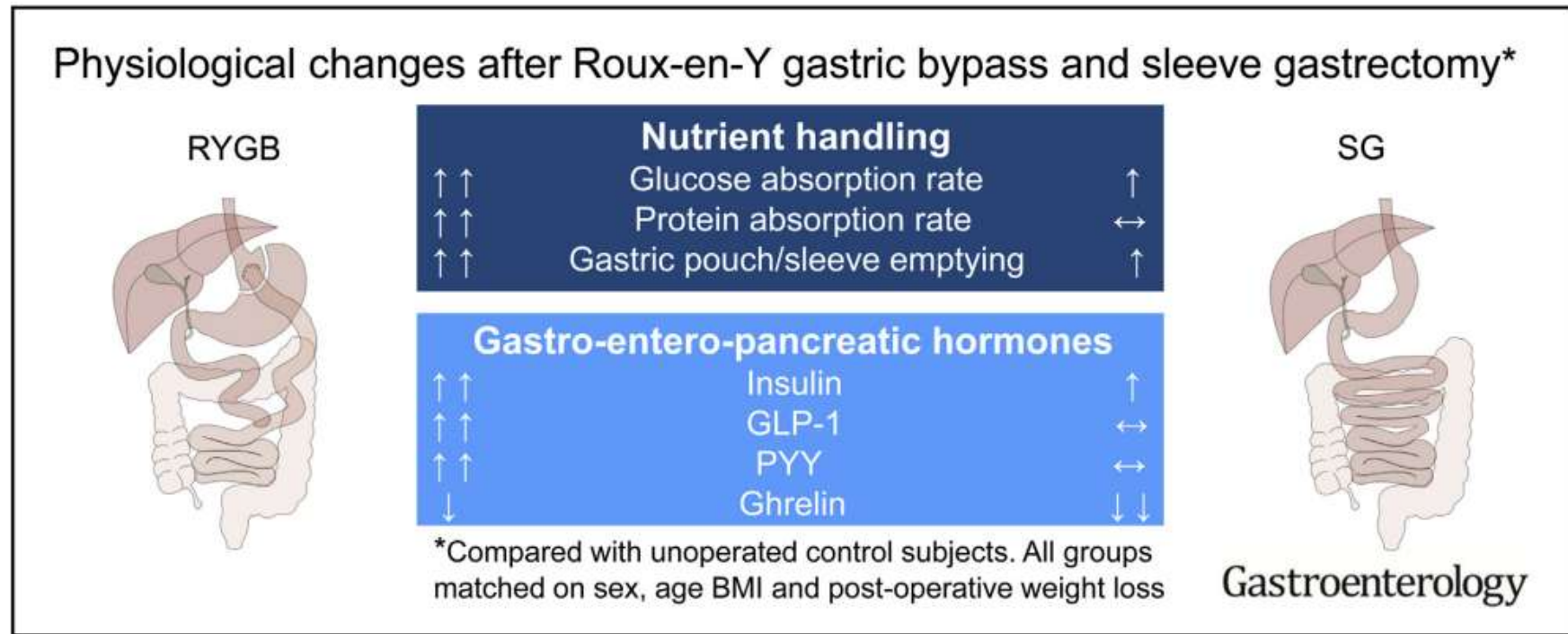
Postprandial Hypoglycemia

Fact or Fiction?

Fred D. Hofeldt, MD; Robert A. Adler, MD; Robert H. Herman, MD

JAMA, Sept 22, 1975—Vol 233, No 12

Upptag efter GBP resp Sleeve

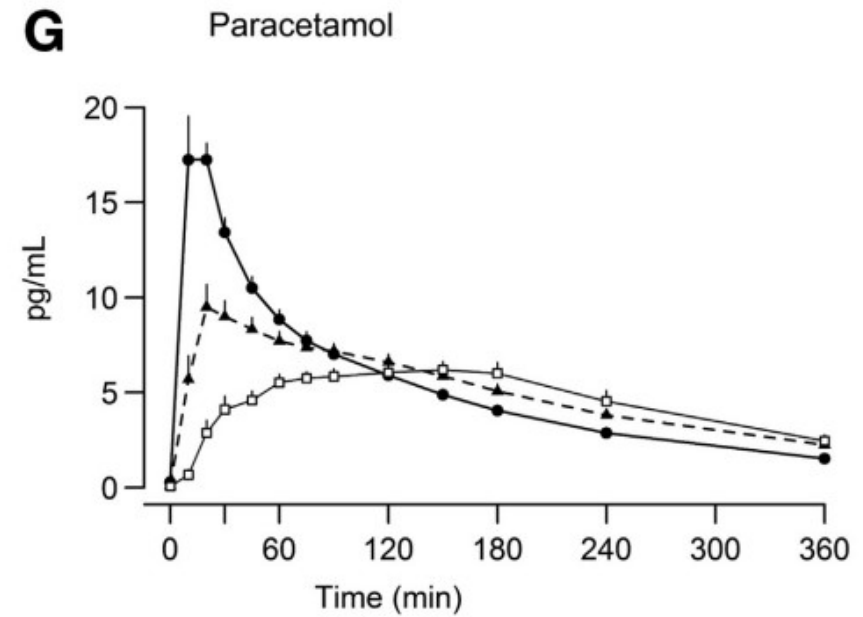
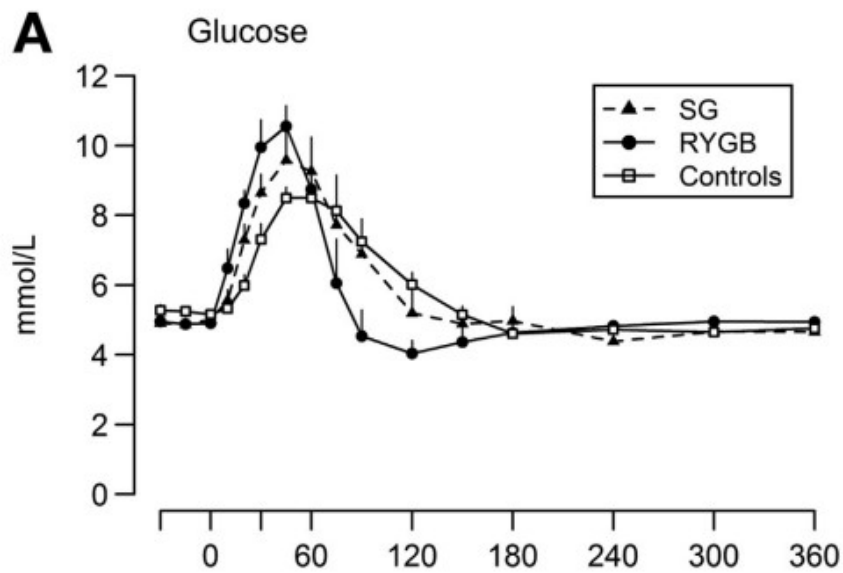


Svane, Madsbad et al

Postprandial Nutrient Handling and Gastrointestinal Hormone

Secretion After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy *Gastroenterology* 2019;156:1627-1641

Upptag efter GBP resp Sleeve



Svane, Madsbad et al

Postprandial Nutrient Handling and Gastrointestinal Hormone Secretion After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy *Gastroenterology* 2019;156:1627-1641

GI Hormoner post GBP resp Sleeve över tid

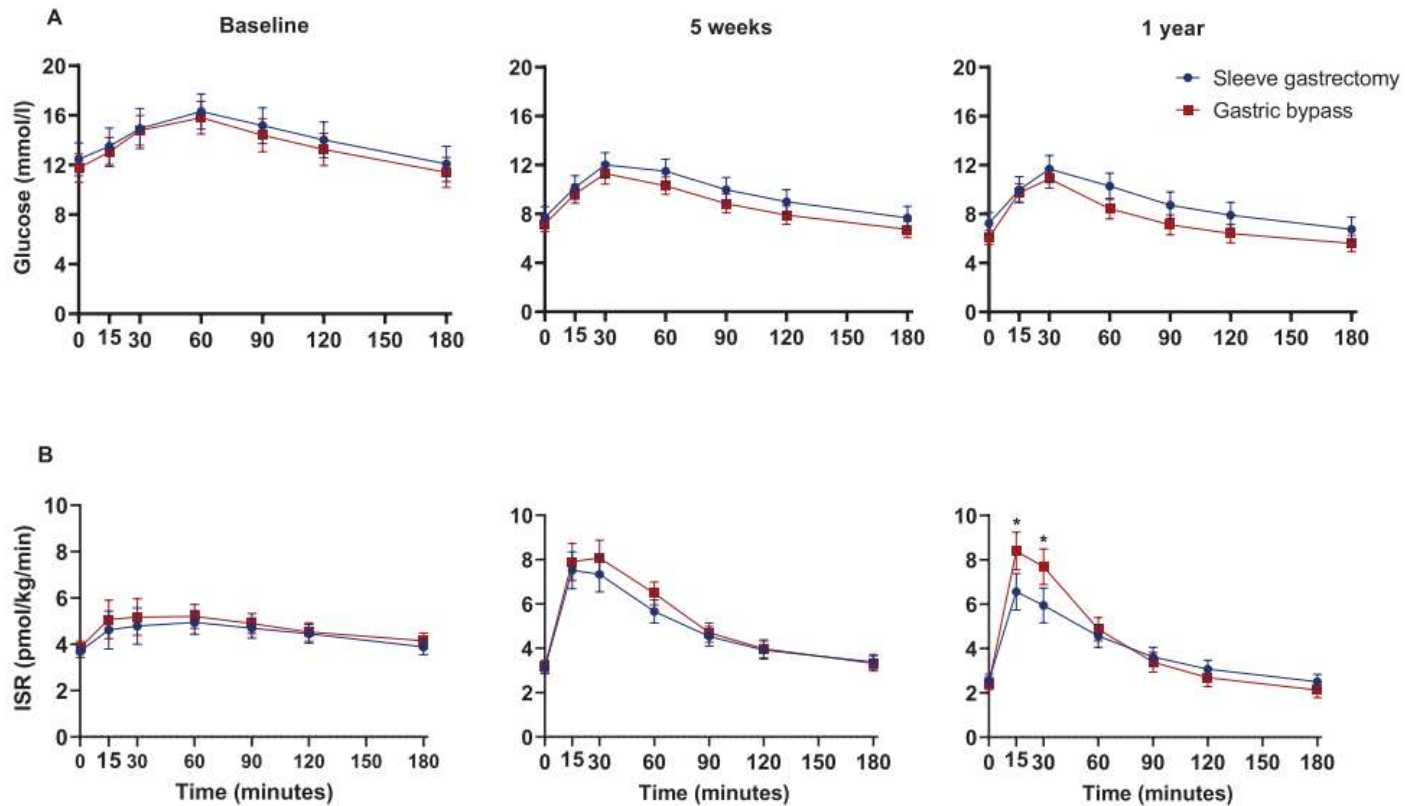


Figure 1. Glucose (A) and prehepatic insulin secretion rates-ISR (B) during oral glucose tolerance tests in patients undergoing sleeve gastrectomy and gastric bypass at baseline, 5 weeks, and 1 year. Plots are mean and 95% CI from linear mixed effects models for repeated measures, * $P < 0.01$ for between-group difference reported for time points showing significant group \times time interaction.

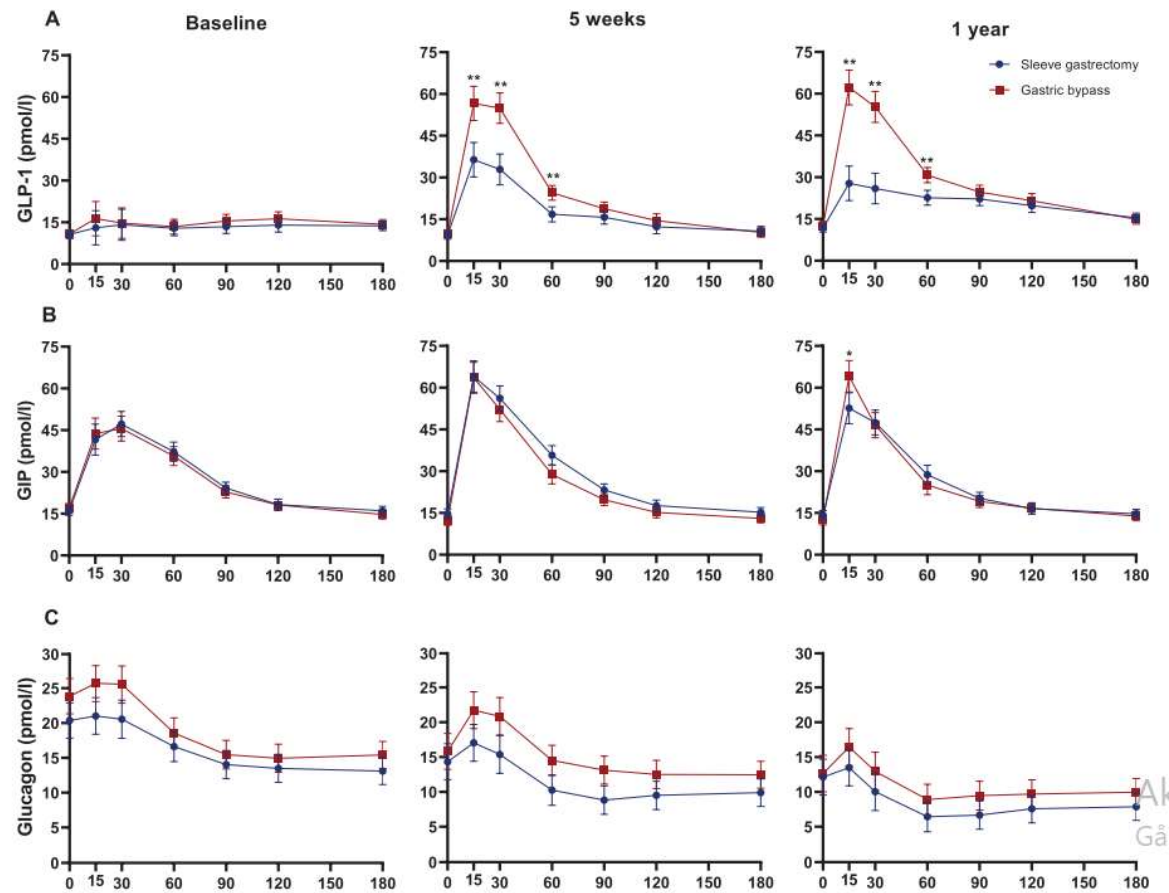
T2dm
n106
randomiserade
50:50

Fatima, Hofse et al

Gastrointestinal Hormones and β -Cell Function After Gastric Bypass and Sleeve Gastrectomy: A Randomized Controlled Trial (Oseberg)

The Journal of Clinical Endocrinology & Metabolism, 2022, Vol. 107, No. 2, e756–e766

GI Hormoner post GBP resp Sleeve över tid

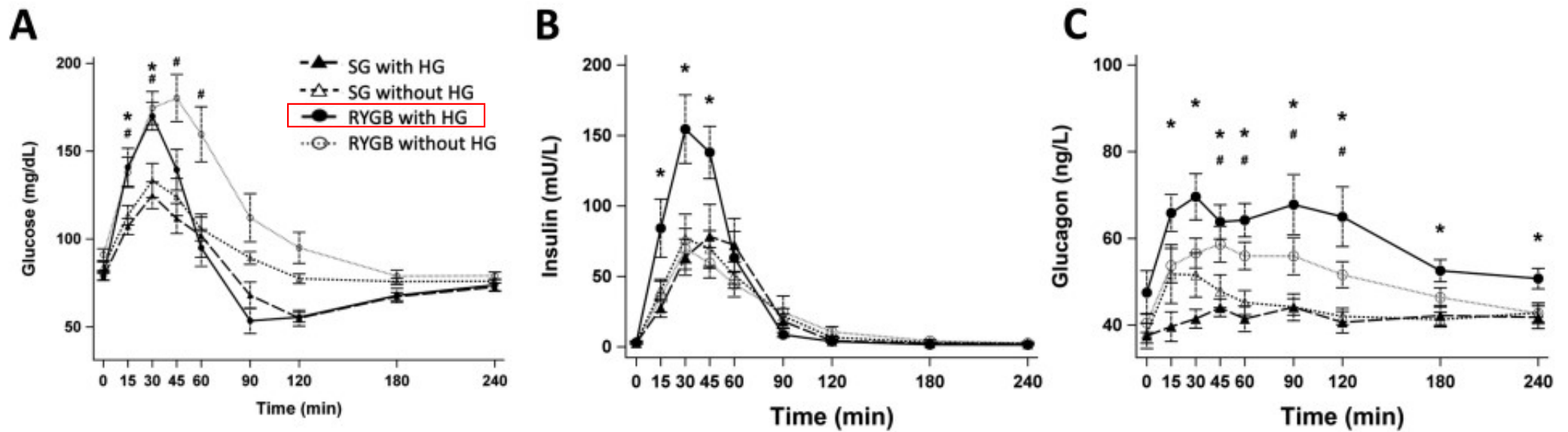


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**Gastrointestinal Hormones and β -Cell Function
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Hormonsvar post GBP resp Sleeve uppdelat i pat med och utan hypoglykemi



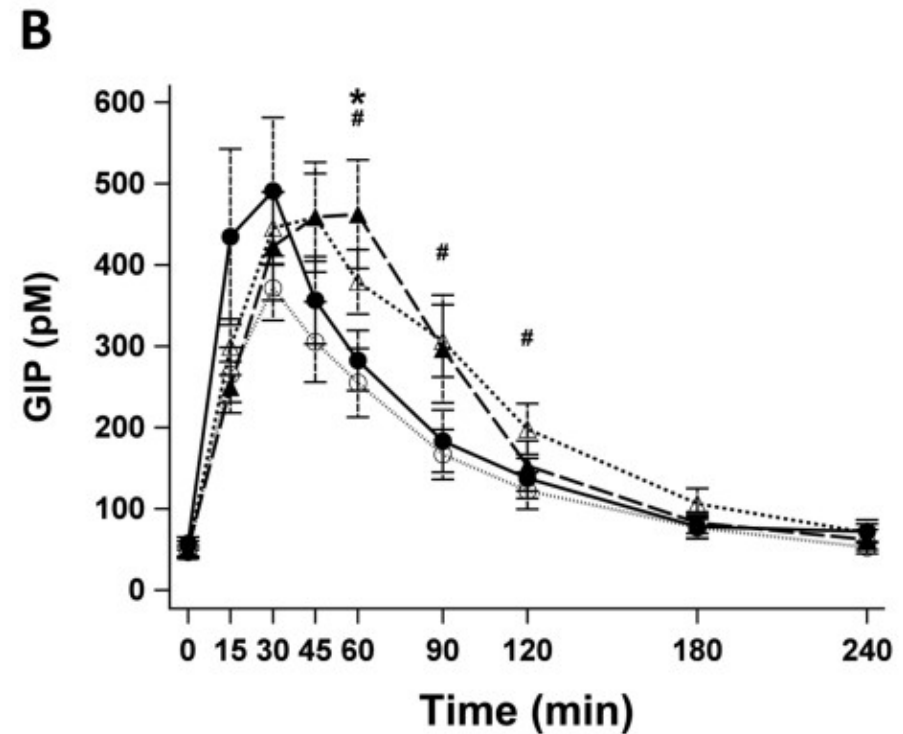
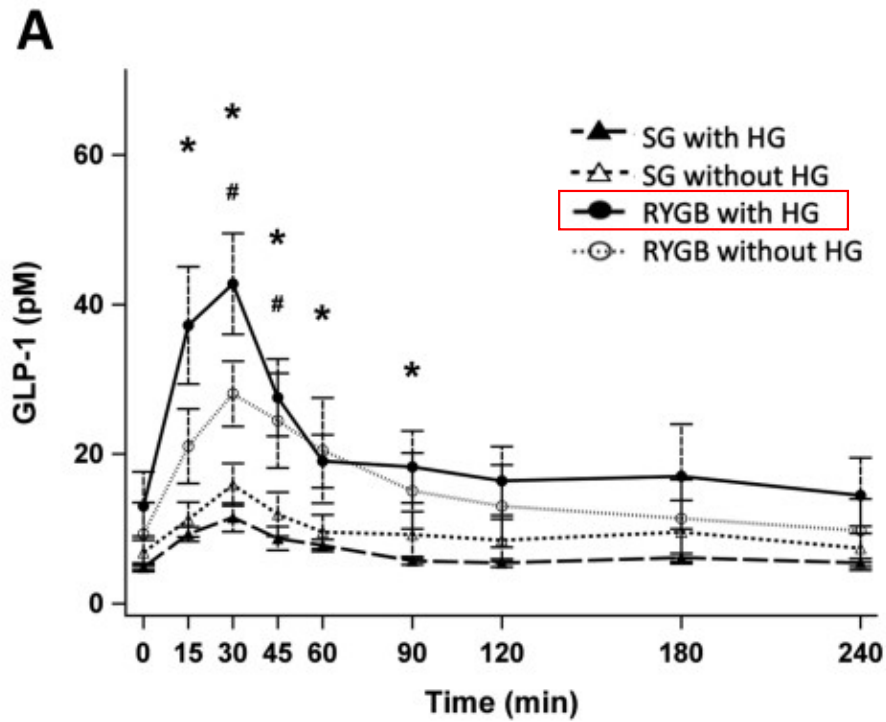
n43

Lee, Brown et al

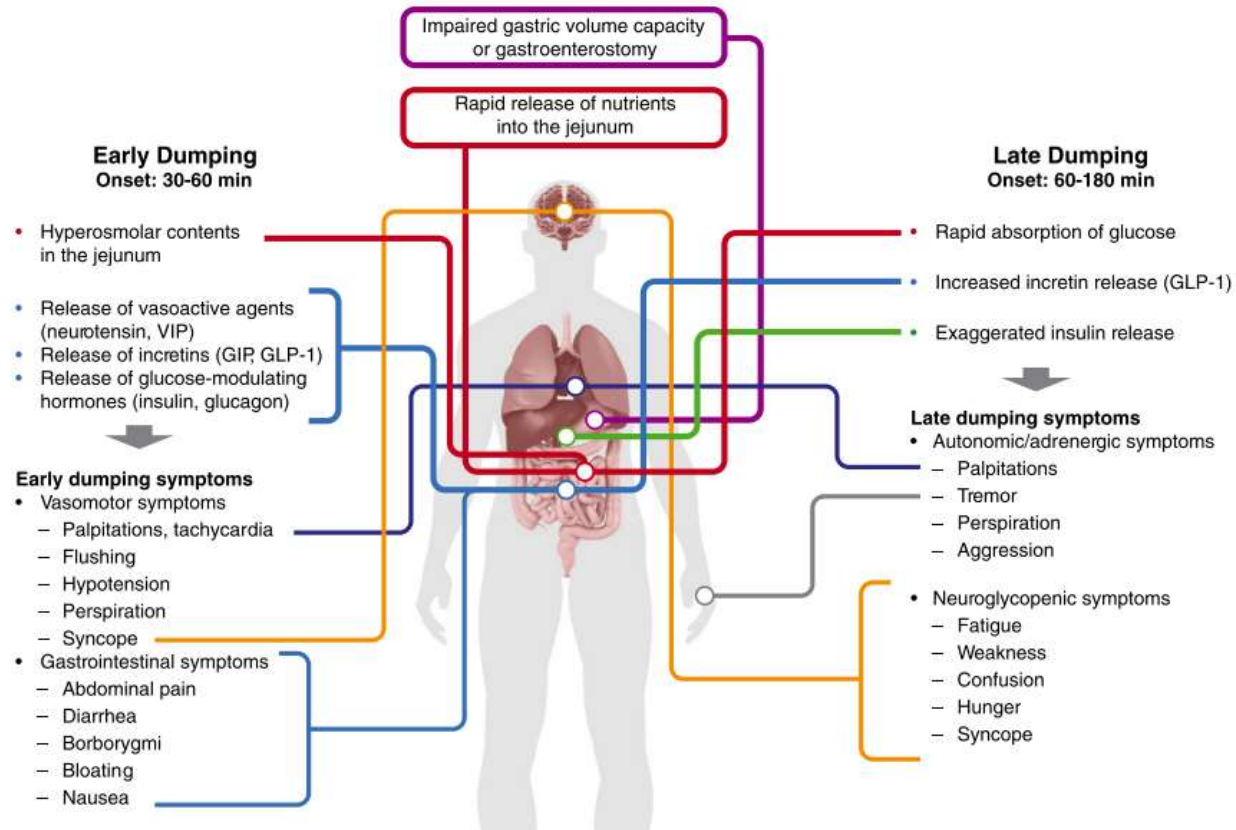
Comparison of Hormonal Response to a Mixed-Meal Challenge in Hypoglycemia After Sleeve Gastrectomy vs Gastric Bypass

The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, e4159–e4166

Hormonsvar post GBP resp Sleeve uppdelat i pat med och utan hypoglykemi



Tidig och sen dumping

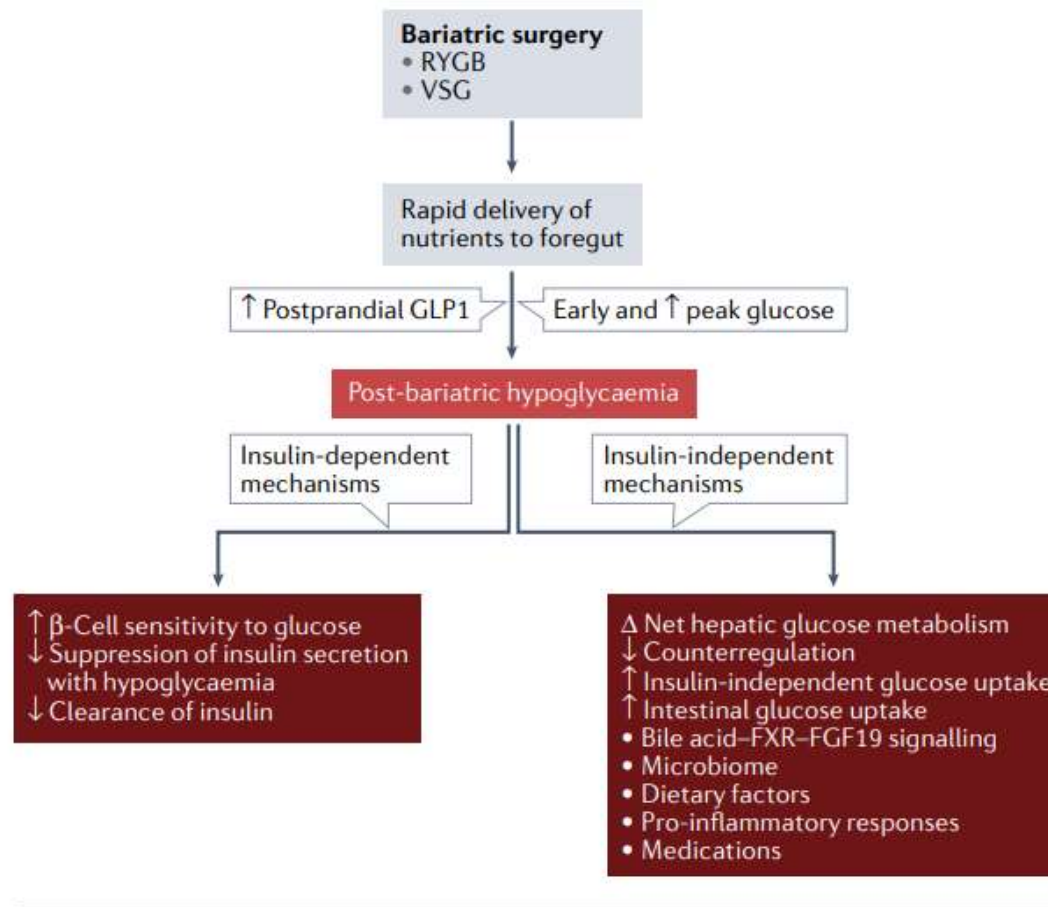


van Beek, Tack et al

Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management

Obesity Reviews 18, 68–85, January 2017

Orsaker till postprandiell hypoglykemi

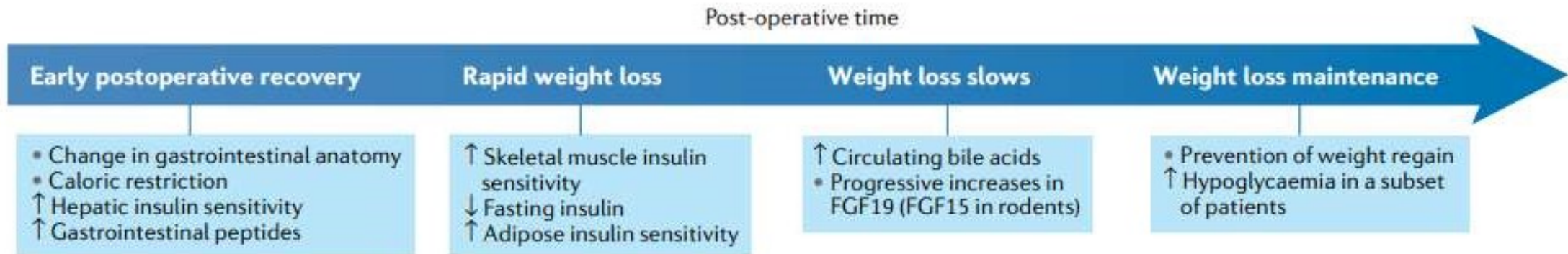


Glucose metabolism after bariatric surgery: implications for T2DM remission and hypoglycaemia

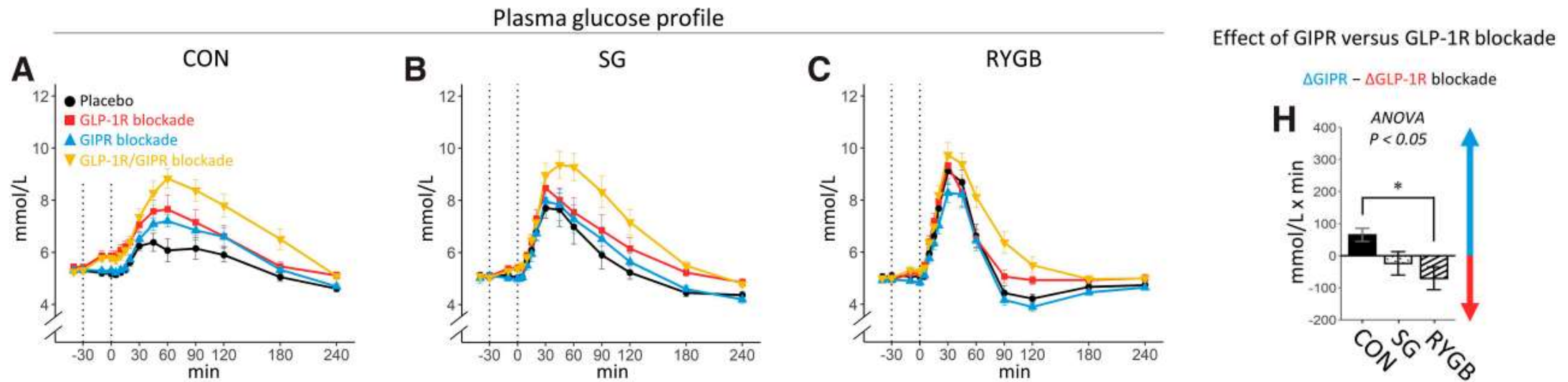
Sandoval, Patti

Nature Reviews Endocrinology | Volume 19 | March 2023 | 164-176

Orsaker till postprandiell hypoglykemi



GLP-1 och GIPs relativa roller

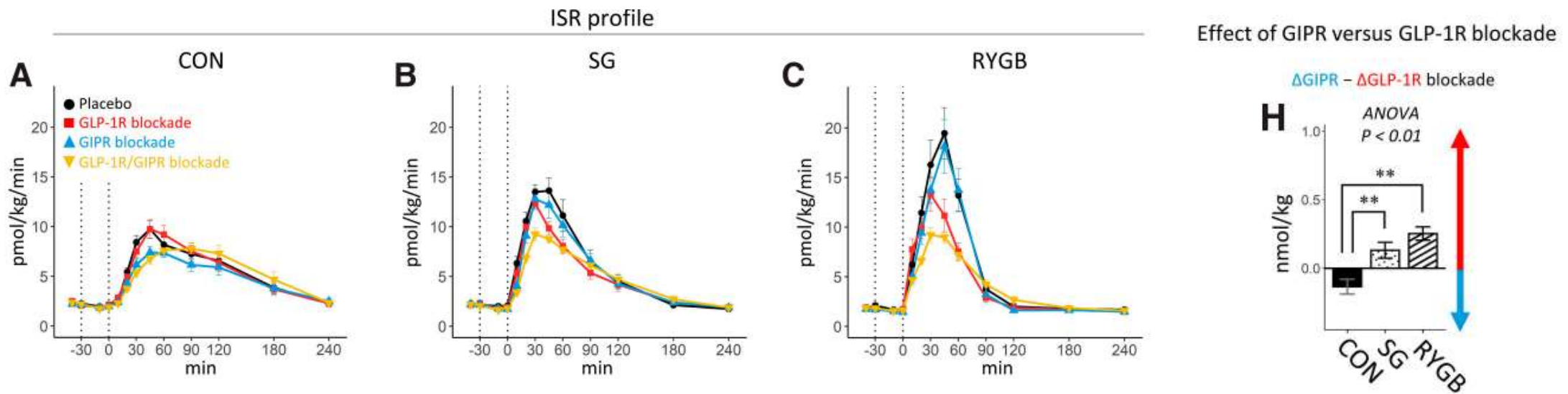


Hindsö, Bojsen-Möller et al

The Importance of Endogenously Secreted GLP-1 and GIP for Postprandial Glucose Tolerance and β -Cell Function After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy Surgery

Diabetes Volume 72, March 2023

GLP-1 och GIPs relativa roller



Hindsö, Bojsen-Möller et al

The Importance of Endogenously Secreted GLP-1 and GIP for Postprandial Glucose Tolerance and β -Cell Function After Roux-en-Y Gastric Bypass and Sleeve Gastrectomy Surgery

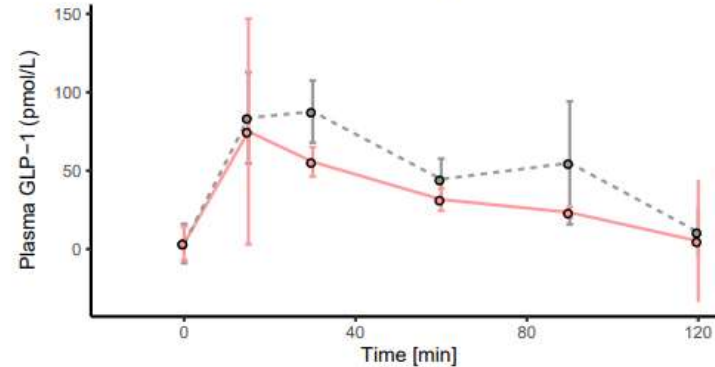
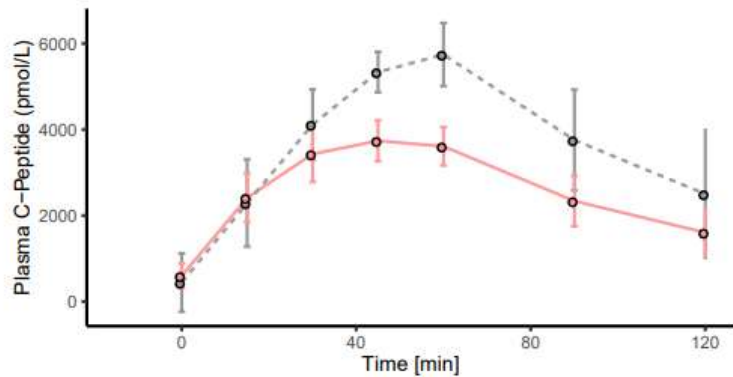
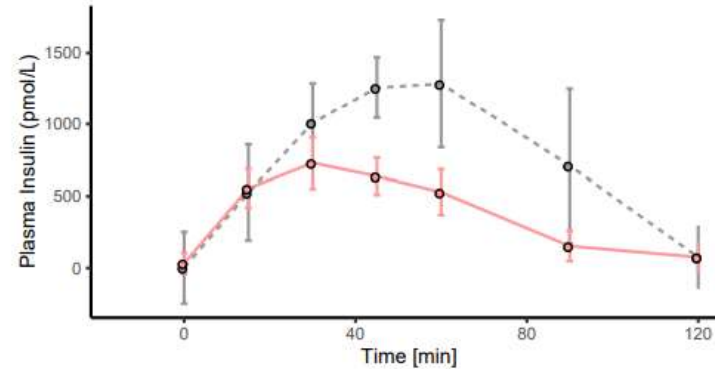
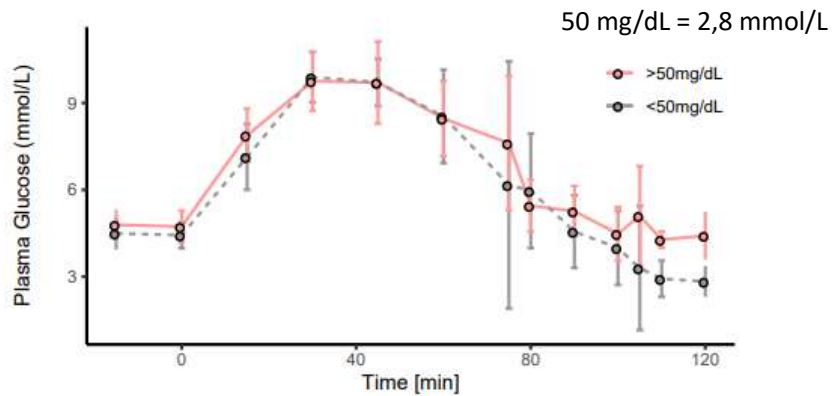
Diabetes Volume 72, March 2023

GLP-1 och GIPs relativa roller

Författarna konkluderar:

- **GIP viktigaste inkretinhormonet vid normalanatomi**
- **GIP/GLP-1 lika viktiga efter Sleeve-operation**
- **GLP-1 viktigaste inkretinhormonet efter GBP-operation**

Är GLP-1 viktigaste faktorn för hypoglykemi?



n25 post-GBP
75g glukos po

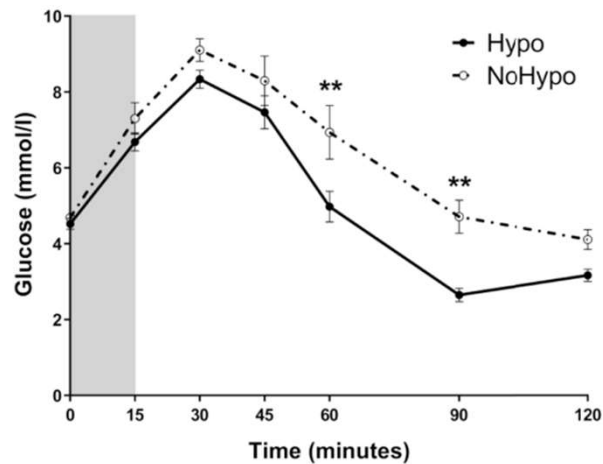
Högt insulinsvar med postprandiell hypoglykemi relaterat till glukos-känslighet mer än till GLP-1

[Surgery for Obesity and Related Diseases 19 \(2023\) 467–472](#)

Unraveling, contributing factors to the severity of postprandial hypoglycemia after gastric bypass surgery Herzig, Bally et al

Glukagons roll i att motverka PPHG

n23, post-GBP, mixed meal test, med hypo resp utan



Snabbt och högt glukagonsvar motarbetar insulinpeaken och förhindrar hypoglykemin – stor individuell variation

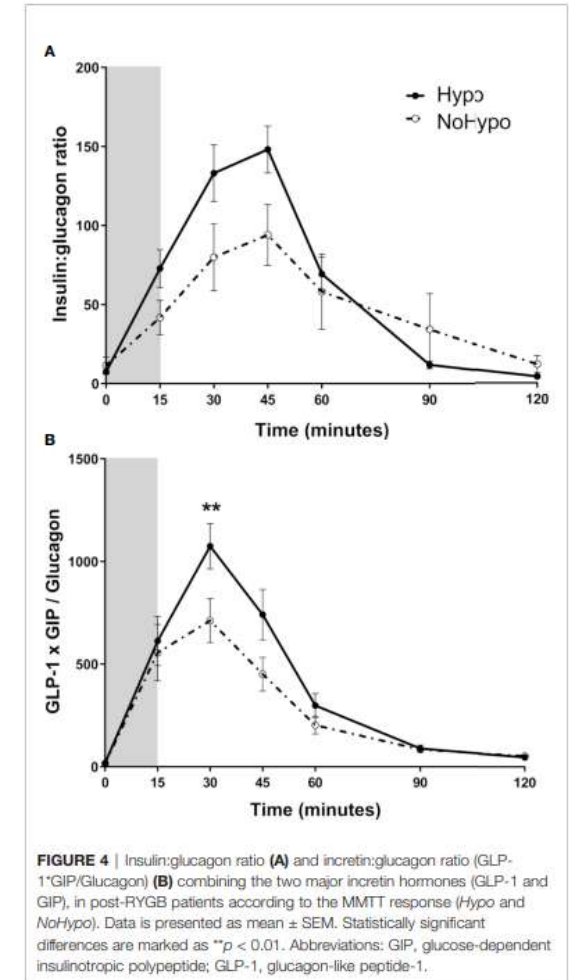
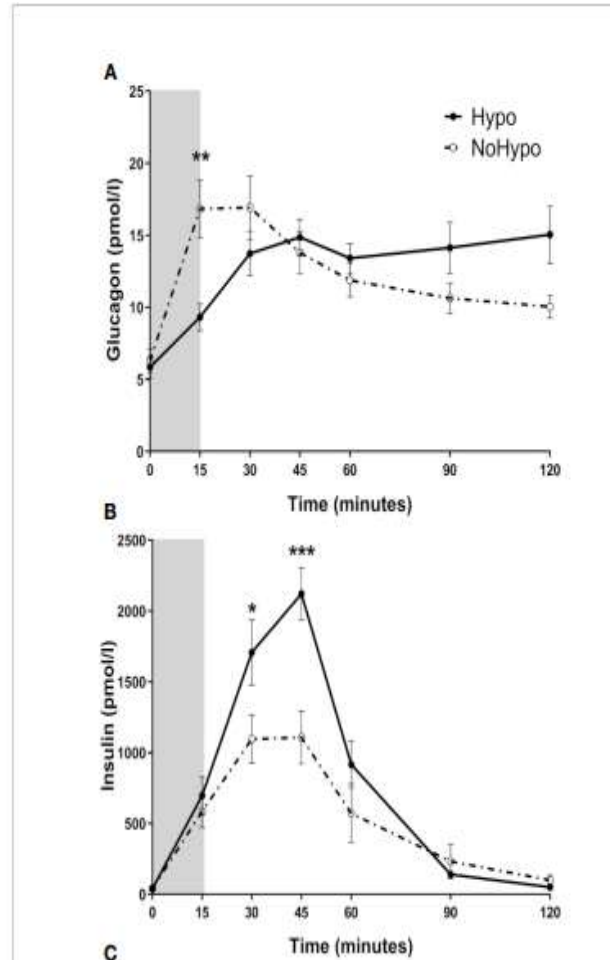


FIGURE 4 | Insulin:glucagon ratio (A) and incretin:glucagon ratio (GLP-1*GIP/Glucagon) (B) combining the two major incretin hormones (GLP-1 and GIP), in post-RYGB patients according to the MMTT response (Hypo and NoHypo). Data is presented as mean ± SEM. Statistically significant differences are marked as ***p* < 0.01. Abbreviations: GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

Relation till partiell tunntarmsobstruktion

Av 80 patienter som behandlades för PP hypoglykemi:

- 38 opererades för sammanväxningar resp rekonstruktion jejunum-jejunostomin
- Av dessa använde 21 medicin mot PPHG, 19 kunde sluta med denna

Författarna föreslår koppling mellan PPHG och partiell tunntarmsobstruktion

Possible relation between partial small
bowel obstruction and severe postprandial
reactive hypoglycemia after Roux-en-Y
gastric bypass

[Anna Laurenus R.D., Ph.D.](#), [Suzanne Hedberg M.D.](#),
[Torsten Olbers M.D., Professor](#)

Surgery for Obesity and Related
Diseases

Volume 15, Issue 6, June 2019, Pages 1024-1028

Hur vanligt är det med postprandiella hypoglykemier?

TABLE 1 Prevalence of hypoglycemia after Roux-en-Y gastric bypass surgery

Method of ascertainment	Prevalence (%) or duration	References
Hospitalization	0.1-1	Marsk et al., ^a Gribsholt et al., ^b Lee ^c
Clinical recognition	0.4-7.6	Gribsholt et al., ^b Kellogg et al. ^d
Severe hypoglycemia requiring assistance (self-report)	11.6	Lee et al. ^e
Symptoms (survey)	33-38, or 0.1	Gribsholt et al., ^b Lee et al., ^e Sarwar et al. ^f
OGTT glucose below 50-60 mg/dL	10-68	Pigeyre et al., ^g Roslin et al. ^h
MMTT glucose below 55 mg/dL	22-29	Kefurt et al., ⁱ Goldfine et al. ^j
CGMS sensor glucose below 55 mg/dL	75	Kefurt et al. ⁱ
CGMS sensor glucose below 60 mg/dL	29-71 min	Kefurt et al., ^{i,k} Halperin et al., ^l Abrahamsson et al., ^m Hanaire et al., ⁿ Ritz et al. ^o

Vad är betydelsefull hypoglykemi?

- n40 med PPHG
- hypoglykemiprovokation med prover och symptomregistrering
- CGM i 20 dagar med symptomdagbok
- Neuroglykopena symtom sign ökat med glukos <3,0mmo/L både under test och CGM
- 37% unawareness <3,0mmol/L
- CGM fångade 10 ggr fler event (<3,0mmo/L) än pats dagböcker

Författarna föreslår <3,0mmo/L som definitionsgräns för betydelsefull postprandiell hypoglykemi

Defining clinically important hypoglycemia in patients with postbariatric hypoglycemia

Craig, McLaughlin
Surgery for Obesity and Related Diseases

Volume 17, Issue 11, November 2021, Pages 1865-1872

Hur många har betydelsefull hypoglykemi?

- n6024
- Ngt glukosvärde postoperativt <3,9mmol/L
- 1,4% symtomatisk hypoglykemi-83st
 - 32/83 hyperinsulinem hypoglykemi, medeldebut 790 dagar postop, 53% erhöill medicinsk beh
 - *8/83 infektion*
 - *8/83 diabetesmedicin*
 - *8/83 åt undermåligt*

Prediktorer för PPHG

- Mixed meal test
- **Lägre HbA1c** lägre resp **större postop viktning** faller ut

Författarna föreslår en score
 ”Viktning/HbA1c” som prediktor för
 PPHG

Variable	Unit	Non-hypoglycemia	Hypoglycemia	<i>p</i>
<i>n</i>		16	19	
Age	years	40.8 (37.5, 47.8)	42.9 (35.4, 51.0)	0.947
Years since surgery	years	4.5 (2.9, 6.4)	3.9 (1.7, 5.5)	0.175
Sex (female)		14 (87.5)	16 (84.2)	1.000
T2DM pre-surgery		2 (14.3)	2 (12.5)	1.000
T2DM current		0 (0)	0 (0)	1
Weight pre-surgery	kg	109.5 (103.8, 121.5)	116.2 (107.5, 129.5)	0.296
Weight current	kg	78.5 (69.0, 91.0)	78.7 (68.8, 82.5)	0.619
Absolute weight loss	kg	29.0 (25.0, 35.2)	39.0 (31.6, 53.5)	0.024
Relative weight loss	%	28.3 (23.1, 30.8)	35.0 (27.7, 45.6)	0.024
BMI pre-surgery	kg/m ²	39.4 (38.1, 42.6)	43.4 (39.8, 45.6)	0.132
BMI current	kg/m ²	28.3 (25.8, 31.8)	28.2 (24.7, 30.3)	0.436
Change in BMI	kg/m ²	10.9 (9.7, 12.8)	14.5 (10.9, 19.5)	0.028
Relative change in BMI	%	28.3 (23.1, 30.8)	35.0 (27.7, 45.6)	0.024
Systolic blood pressure	mmHg	119.0 (115.5, 131.5)	109.0 (100.0, 117.0)	0.060
Diastolic blood pressure	mmHg	80.0 (68.8, 82.5)	71.0 (68.0, 81.0)	0.462
Heart rate	min ⁻¹	74.5 (66.0, 81.2)	72.0 (68.0, 80.0)	0.723
Baseline glucose	mmol/l	4.7 (4.4, 4.8)	4.5 (4.5, 4.7)	0.485
Baseline insulin	mU/l	5.5 (3.5, 8.5)	6.0 (4.3, 9.6)	0.832
Baseline C-peptide	pmol/l	609.0 (519.8, 739.5)	693.5 (579.8, 740.0)	0.512
HbA _{1c}	%	5.3 (5.0, 5.7)	4.9 (4.7, 5.2)	0.009
Hemoglobin	g/l	133.0 (126.8, 145.5)	126.5 (122.2, 135.8)	0.097
C-reactive protein	mg/l	0.6 (0.4, 2.0)	0.7 (0.3, 1.6)	0.637
Glomerular filtration rate	ml/min/1.7	99.0 (86.2, 112.0)	103.5 (99.2, 111.2)	0.333
HOMA-IR		1.2 (0.7, 1.8)	1.3 (0.9, 2.1)	0.401
HOMA-beta		81.3 (53.0, 124.2)	127.7 (84.0, 159.4)	0.139
HOMA2-IR		1.3 (1.2, 1.5)	1.4 (1.1, 1.5)	0.808
HOMA2-beta		132.1 (110.6, 150.1)	138.8 (123.2, 153.2)	0.612

Relation till viktning

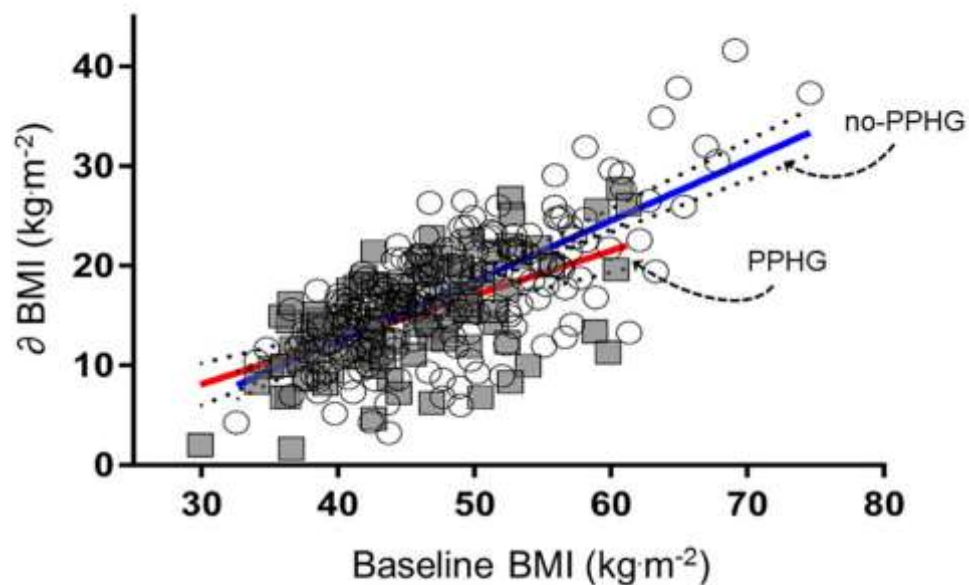
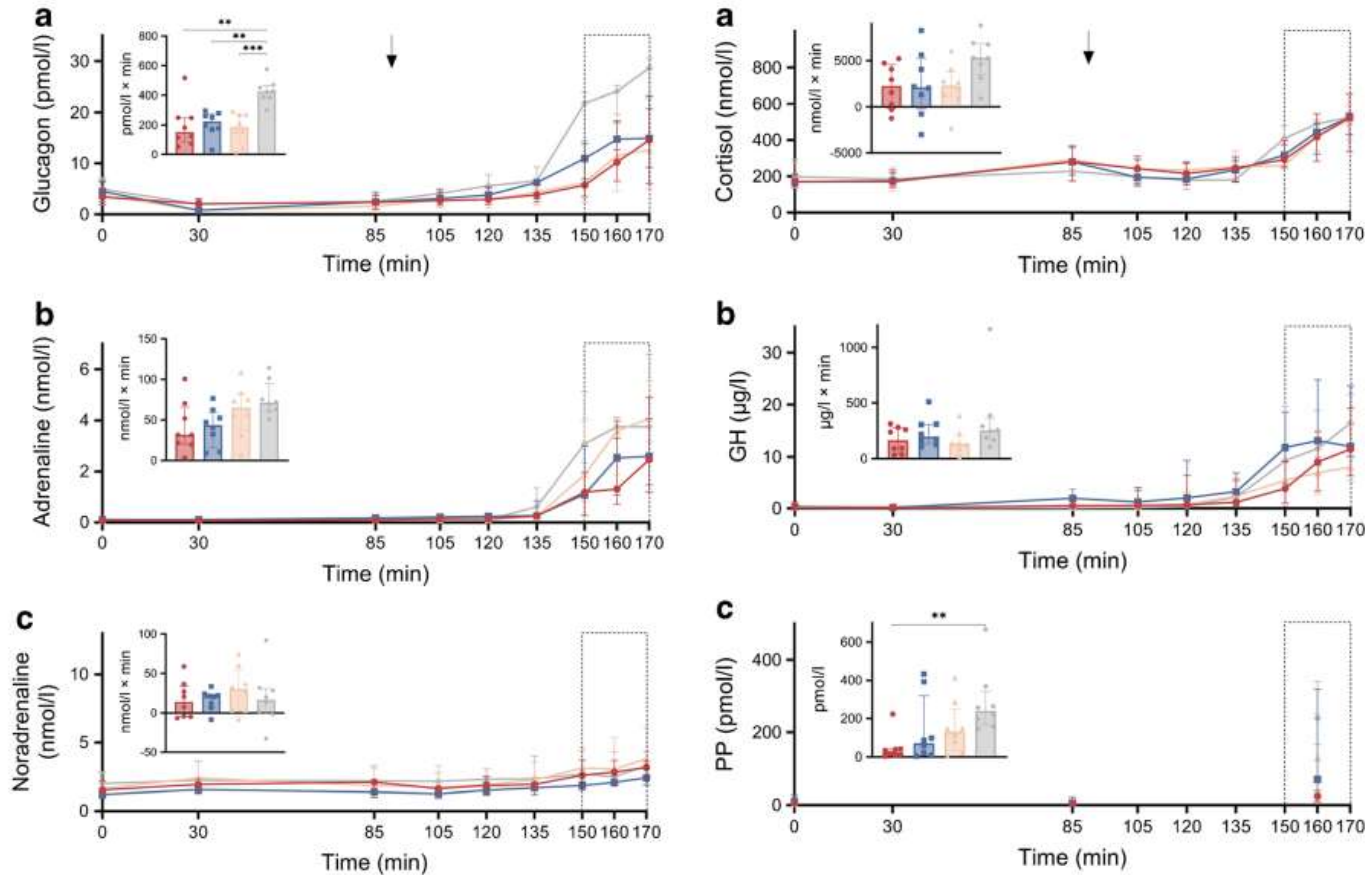


Fig. 2 Association between baseline BMI and change of BMI (Δ BMI) 2 years after surgery in subjects in the PPHG group (*squares*) and the no-PPHG group (*circles*). The slope in the former is significantly ($p = 0.02$) less steep than that in the latter group

Hur väl fungerar motregleringen?



Hypoglykemiclamp
Insulin ges vid pilen

Rött= PPHG
 Blå=GBP ej PPHG
 Gul=Sleeve ej PPHG
 Grå=Control

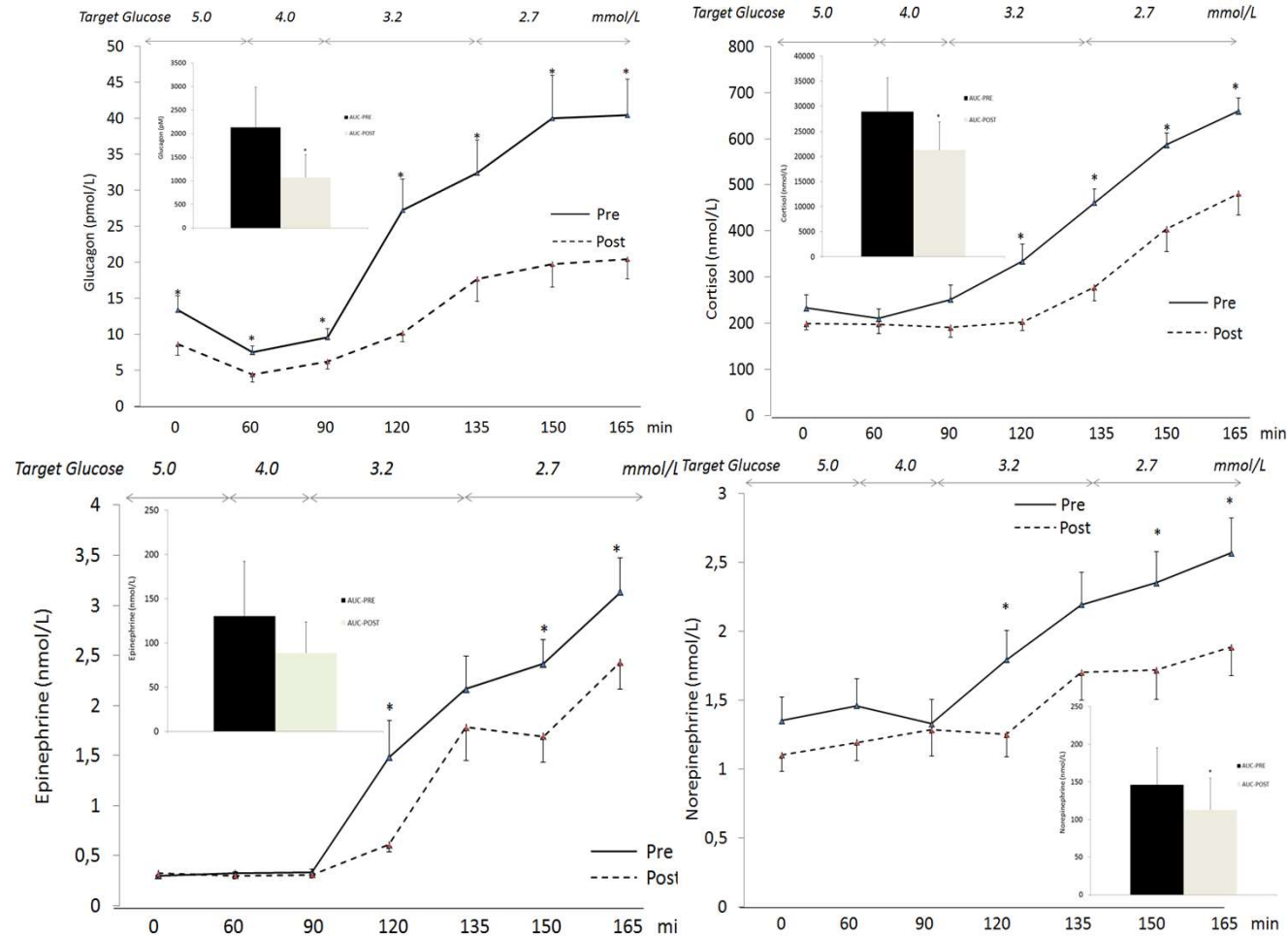
Inuti boxen=hypofas

Fig. 3 Profiles of glucagon (a), adrenaline (b) and noradrenaline (c) over the entire experiment. Data are presented as median (IQR). The arrow shows the initiation of insulin aspart infusion (t90) and the rectangles with the dotted line correspond to the hypoglycaemic period (t150–t170). The bar charts indicate the iAUC of the respective hormone during t150–t170 (relative to t85) and show the individual data as well as the median values (top of the bar) and the IQR (whiskers). Red circles, PBH group (n=8); blue squares, RYGB control group (n=8); orange triangles, SG control group (n=8); grey diamonds, CN (n=8). **p<0.01 and ***p<0.001 in the post hoc analysis

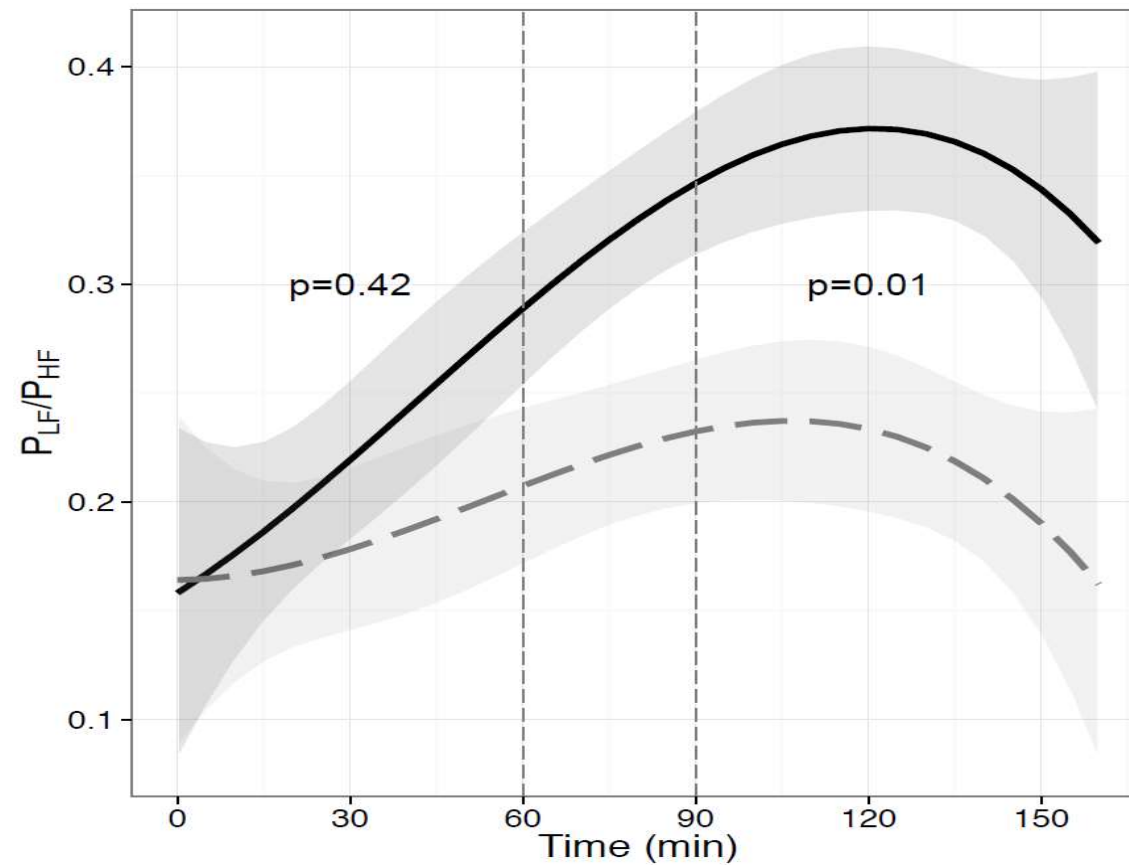
Counter-regulatory responses to postprandial hypoglycaemia in patients with post-bariatric hypoglycaemia vs surgical and non-surgical control individuals

Tripyla, Bally et al Diabetologia (2023) 66:741–753

Motreglering pre och postop, GBP, inga symtom på PPHG



Motreglering pre och postop, GBP, inga symtom på PPHG



Sympatikus mätt som HRV

Bör man testa för PPHG på alla patienter?

- n113 post-GBP
- Kolhydratrik måltid
- 11,5% Hypoglykemi (<3,0mmol/L)
- Varav 5,3% asymtomatiska
- Författarna föreslår screening för alla patienter

Bå linje Glukos

Grön Linje Insulin

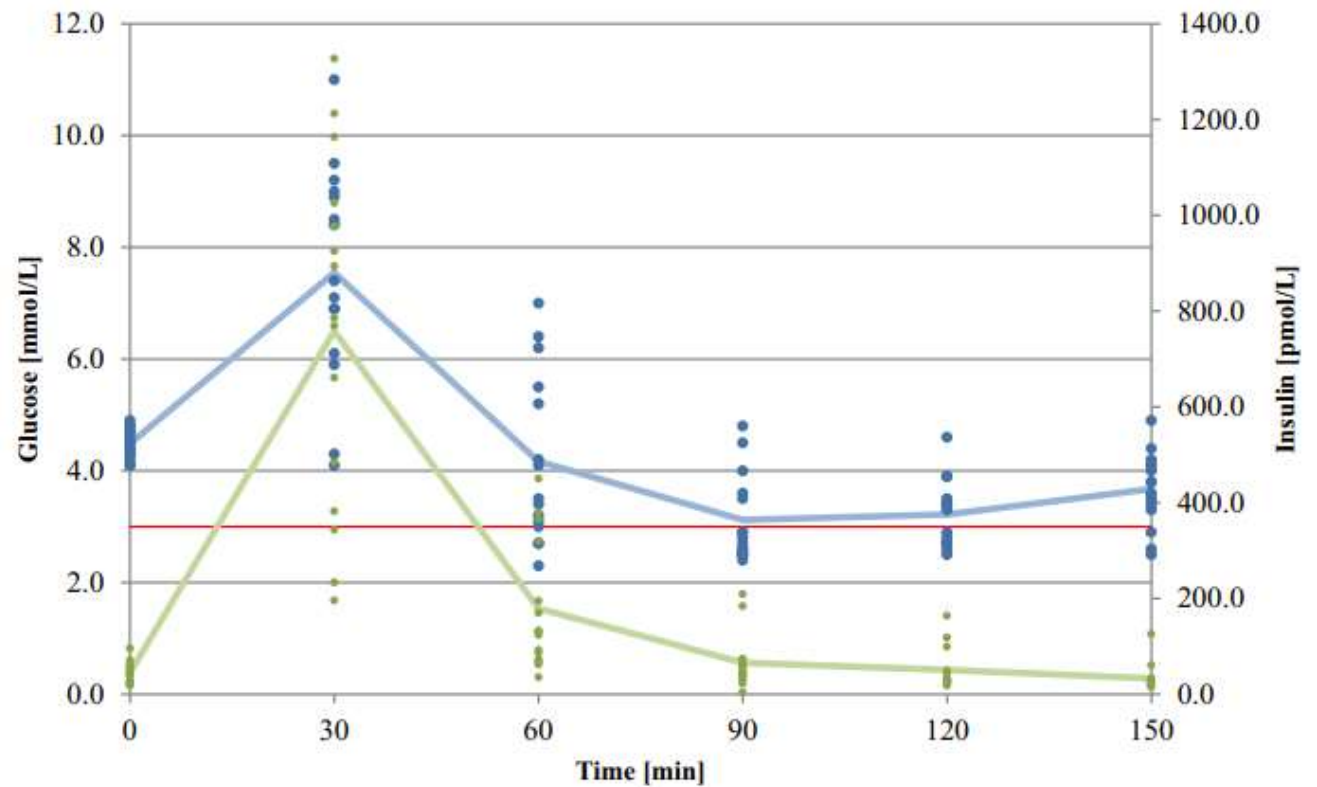


Fig. 2. Plasma-glucose and insulin distribution after the carbohydrate-rich provocative meal in hypoglycemic patients.

Gasser, Stanga et al

[Clinical Nutrition 38 \(2019\) 444–449](#)

Is testing for postprandial hyperinsulinemic hypoglycemia after gastric bypass necessary?

Hur behandlar vi?

ASMBS Position Statement on Postprandial Hyperinsulinemic Hypoglycemia after Bariatric Surgery

Dan Eisenberg, M.D., M.S.^{a,b,*}, Dan E. Azagury, M.D.^c, Saber Ghiassi, M.D.^{d,e},
Brandon T. Grover, D.O.^f, Julie J. Kim, M.D.^g

- Ovanligt tillstånd
- Kan leda till kognitiv och neurologisk nedsättning med risk för krampanfall och medvetandeförlust
- Om faste-hypoglykemi – uteslut insulinom
- Diagnos kräver matdagbok, labprover, och provokationstest tillsammans med symptom minst 1 år postop.
 - #1 behandling dietist- helst specialintresserad
 - #2 behandling remiss till endokrinolog
 - Farmakoterapi
 - En gastrostomi tub i remnant magsäcken för att utvärdera om reop kan vara lyckat.
 - Partiell pankreatektomi rekommenderas ej.

Medicinsk behandling

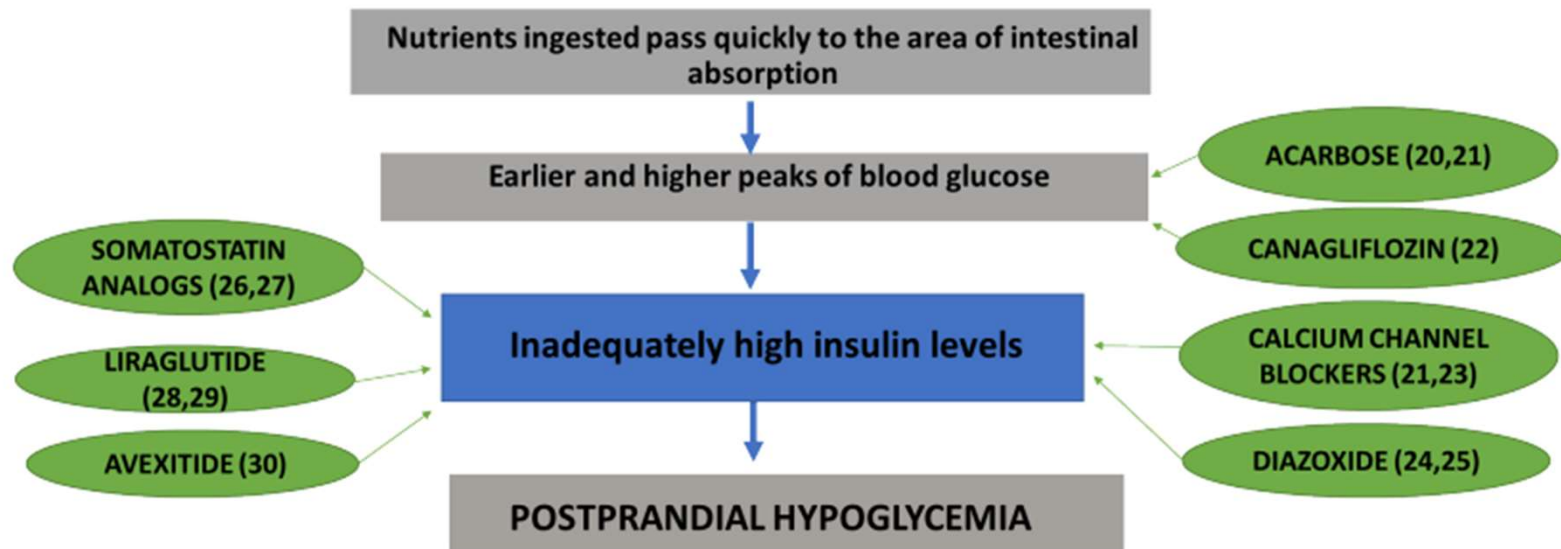


Figure 1. Pathophysiological mechanisms of PPH after BS and mechanisms of action of different therapeutic agents

MEDICATIONS USED FOR THE TREATMENT OF PPH EFFECTIVELY IN CLINICAL TRIALS

ACARBOSE (20,21)

20: n5 i testmeal med o utan. 21: n1 casereport

- Mechanism of action: delays the absorption of carbohydrates, reducing postprandial glycemic and insulinemic peaks.
- Dose: 100 to 300 mg/day before main meals. Start with 25 mg/day and increase gradually
- Side effects: flatulence, diarrhea, abdominal pain.

SOMATOSTATIN ANALOGS (OCTREOTIDE AND PASIREOTIDE) (26,27)

26: n30, 3mån beh, ingen kontrollgrp. 27: n5, testmeal

- Mechanism of action: reduces GLP-1 levels and inhibits insulin secretion
- Dose: octreotide 25 to 50 ug SC before meals; pasireotide SC 75 to 300 mcg/day
- Side effects: diarrhea, steatorrhea, abdominal pain, gallstones, QT interval prolongation, persistent hyperglycemia

CANAGLIFLOZIN (22)

n21, 2v, dubbla OGGT, ingen kontroll

- Mechanism of action: Canagliflozin: reduces carbohydrate absorption by inhibiting intestinal SGLT-1 and thus decreases postprandial insulin spike
- Dose: 300 mg per day
- Side effects: genital infections, volume depletion, increased urinary frequency

AVEXITIDE (currently in phase II of testing) (30)

n19, 3 dagar

- Mechanism of action: GLP-1 receptor antagonists, reduce postprandial insulin and GLP-1 secretion and increase glucagon
- Side effects: Headache, nausea, and subcutaneous injection site reaction.

MEDICATIONS ALREADY USED, HOWEVER, ONLY CASE REPORTS SHOW EFFECTIVENESS

CALCIUM CHANNEL BLOCKERS (VERAPAMIL (21) AND NIFEDIPINE (23))

21: n1 case, 23: n2 case

- Mechanism of action: reduce postprandial insulin secretion
- Dose: verapamil: 80 mg twice a day; nifedipine: 30 mg/day
- Side effects: water retention, hypotension, edema, nausea, headache

DIAZOXIDE (24,25)

24: review alla orsaker, 25: n1 case

- Mechanism of action: activates ATP-dependent potassium channels and decreases the opening of calcium channels, reducing insulin release
- Dose: 50 mg, 2x/day
- Side effects: fluid retention, hypertrichosis, gastrointestinal disorders, edema and neutropenia

LIRAGLUTIDE (28,29)

28: n5 case, 29: n1 case

- Mechanism of action: persistent activation at the GLP-1 receptor leading to inhibition of insulin release and increased glucagon release in hypoglycemic conditions
- Dose: 0.6 mg SC/day initially, progress to 1.2 mg SC
- Side effects: nausea, headache, stomach pains, constipation, diarrhea

GLP-1-beh

Systematisk review

Results and Conclusions: Postprandial hyperinsulinemic hypoglycemia remains a notoriously difficult to manage metabolic complication of bariatric surgery. This first, to the authors' knowledge, systematic review presents evidence suggesting that use of GLP-1RAs does not lead to an increase of hypoglycemic episodes, and, although this approach may appear counterintuitive, the findings suggest that GLP-1RAs could reduce the number of postprandial hypoglycemic episodes and improve glycemic variability.

Obesity (Silver Spring). 2023;31:20–30. Llewellyn, Dimitriadis et al

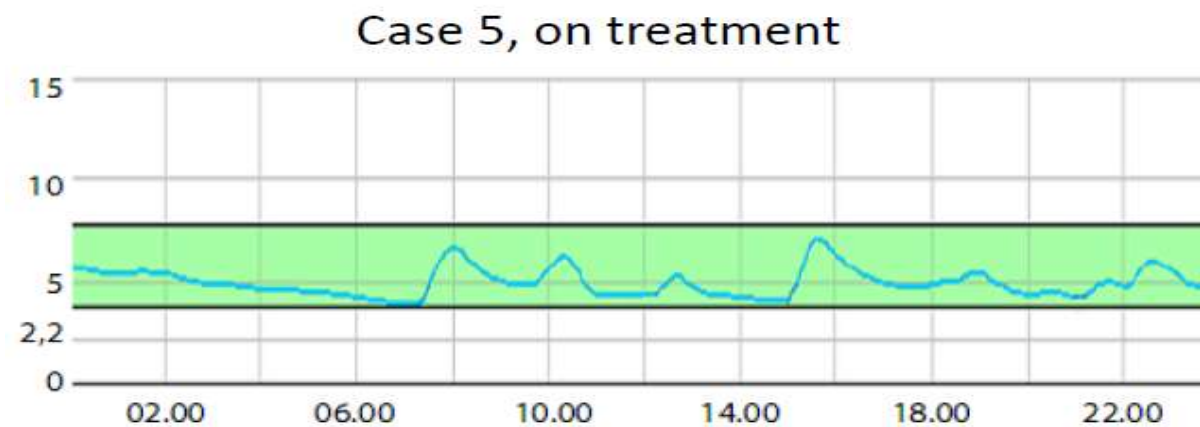
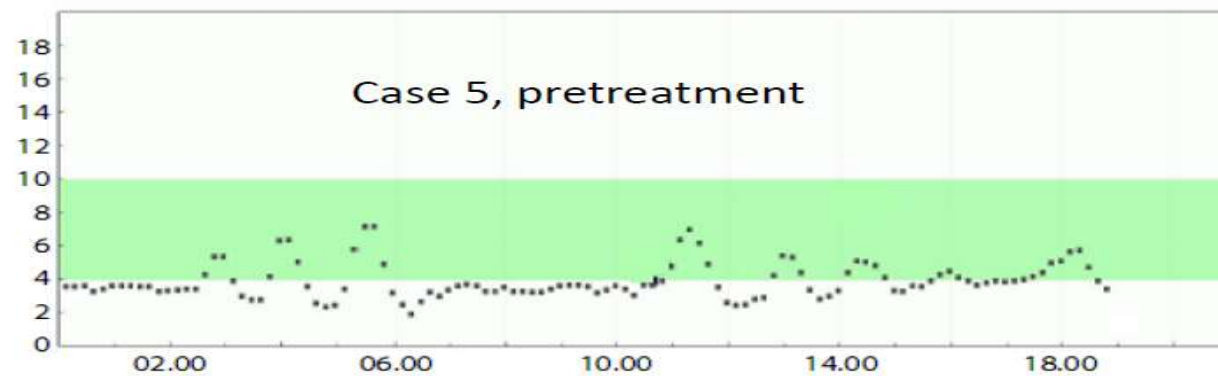
The efficacy of GLP-1RAs for the management of postprandial hypoglycemia following bariatric surgery: a systematic review

TABLE 1 Characteristics of studies using GLP-1 agonists for postprandial hypoglycemia

Study	Country	Study design	Follow-up	Sample size on GLP-1RA (n)
Abrahamsson et al., 2013 [38]	Sweden	Case series	Varied, minimum 6 months	5
Tharakan et al., 2017 [9]	UK	RCT	Not done	1
Øhrstrøm et al., 2019 [7]	Denmark	Randomized crossover study	Not done	11
Almby et al., 2019 [40]	Sweden	Randomized crossover study	Not done	12
Ding et al., 2021 [53]	China	Case report	Not done	1
Shalamar D. Sibley, MD (unpublished data, 2021)	United States	Randomized crossover study	Unknown	11

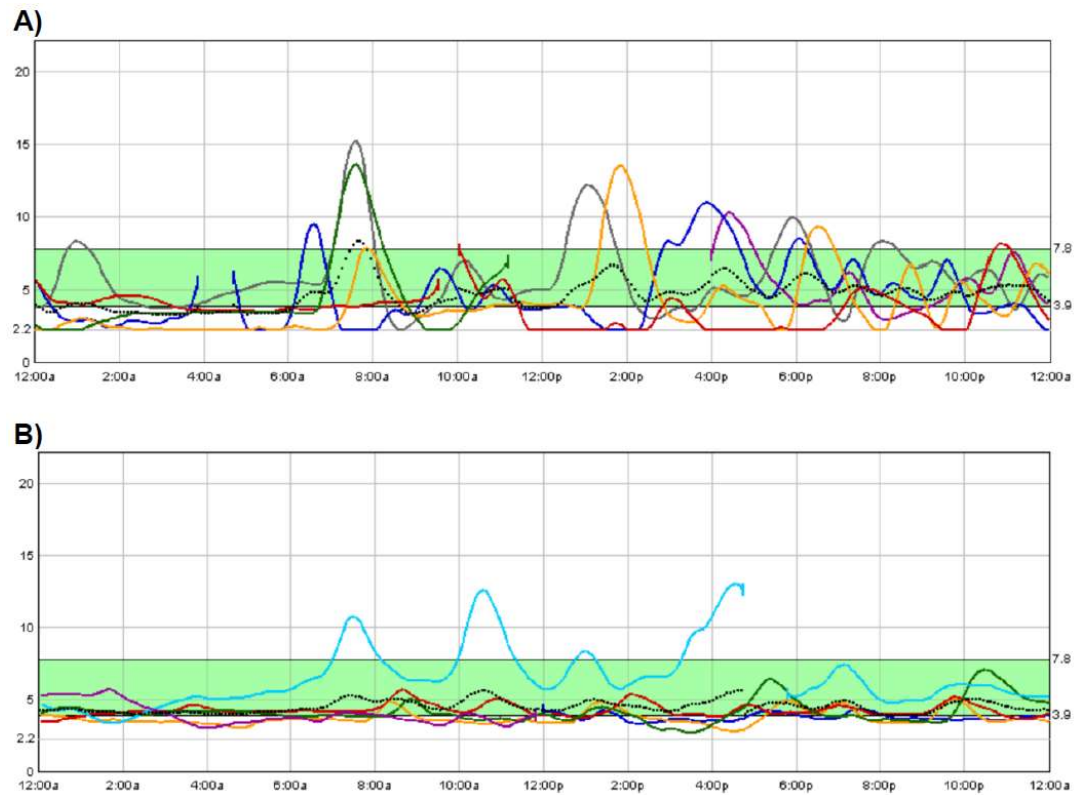
GLP-1-analog-behandling

Post-GBP-pat pre o post Liraglutide behandling.

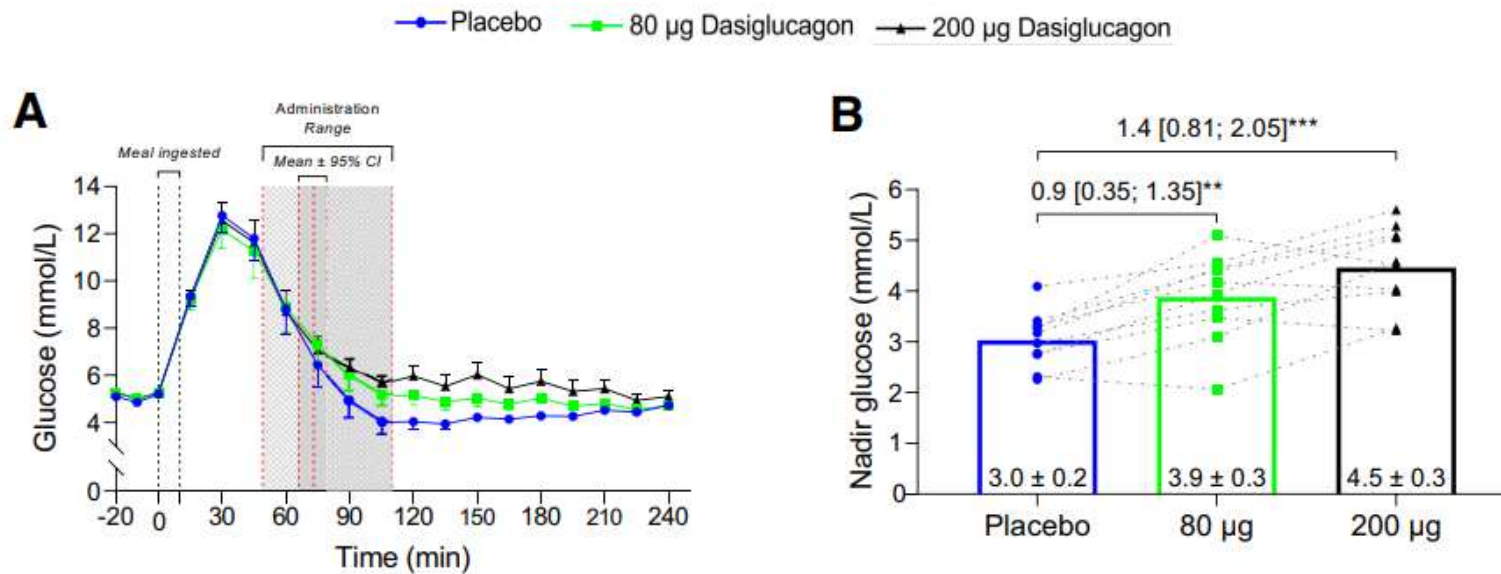


GLP-1-analog-behandling

Post-GBP-pat pre o post Liraglutide behandling.



Glukagon som behandling?



Dasiglucagon Effectively Mitigates Postbariatric Postprandial Hypoglycemia: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

Nielsen, Knop et al

Empagliflozin (Jardiance) som behandling

N=7+7

	HG	NHG	<i>P</i> value
Age (yr)	54.1 ± 10.1	60.7 ± 5.4	0.158
BMI before surgery (kg/m ²)	41.4 ± 4.2	43.1 ± 7.5	0.740
Pre surgery weight (kg)	107.0 ± 9.0	111.4 ± 22.5	0.638
Excess body weight (kg)	42.3 ± 3.6	46.3 ± 7.4	0.644
Maximum total body weight loss (kg)	43.7 ± 9.2	37.2 ± 10.6	0.252
Percent of excess body weight loss(%)	86.0 ± 20.8	64.0 ± 31.5	0.173
Percent recovered from total weight loss(%)	18.2 ± 9.6	27.1 ± 19.4	0.301
Current weight	71.0 ± 6.5	84.1 ± 20.0	0.146
Current BMI (kg/m ²)	27.7 ± 4.2	32.3 ± 6.5	0.185
Time after surgery (yr)	7.8 ± 1.2	8.1 ± 2.4	0.784

Data are presented as mean ± standard deviation

HG, hypoglycemic group; *NHG*, non hypoglycemic group; *BMI*, body mass index

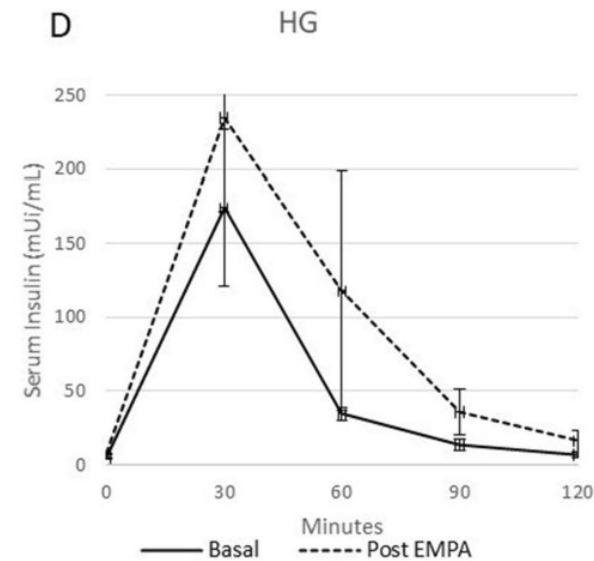
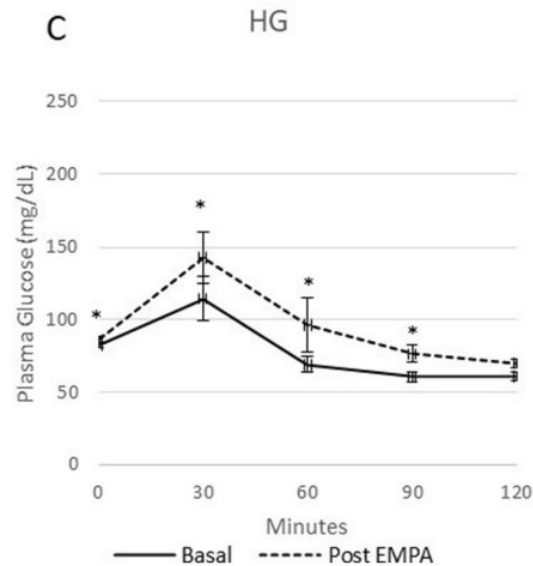
Obesity Surgery (2022) 32:2664–2671

SGLT2 Inhibition with Empagliflozin as a Possible Therapeutic Option for Postprandial Hypoglycemia After Bariatric Surgery

Carpentieri, Zanella et al

Empagliflozin som behandling

-Meal tolerance test



Conclusion Our results suggest that empagliflozin increased glycemic levels in patients with PPH possibly through increases in hepatic glucose production.

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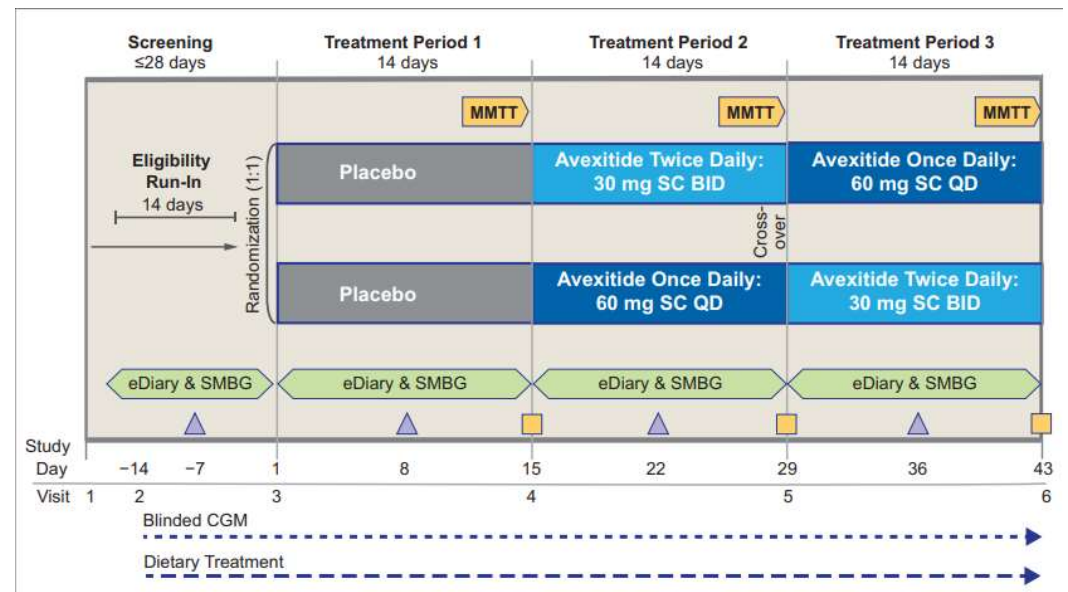
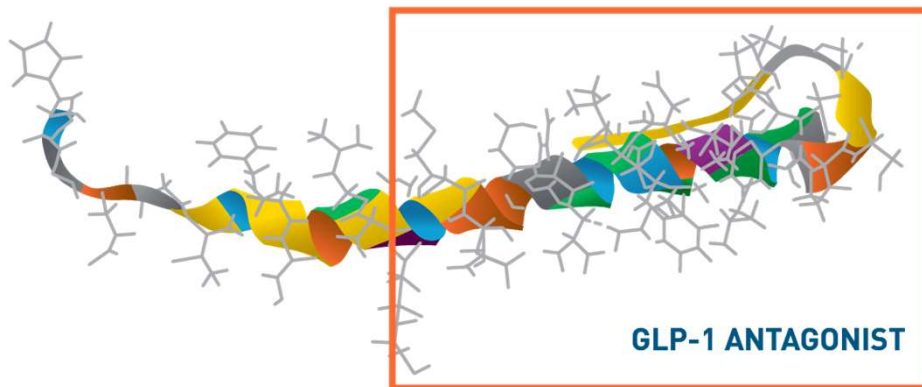
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PREVENT: A Randomized, Placebo-controlled Crossover Trial of Avexitide for Treatment of Postbariatric Hypoglycemia

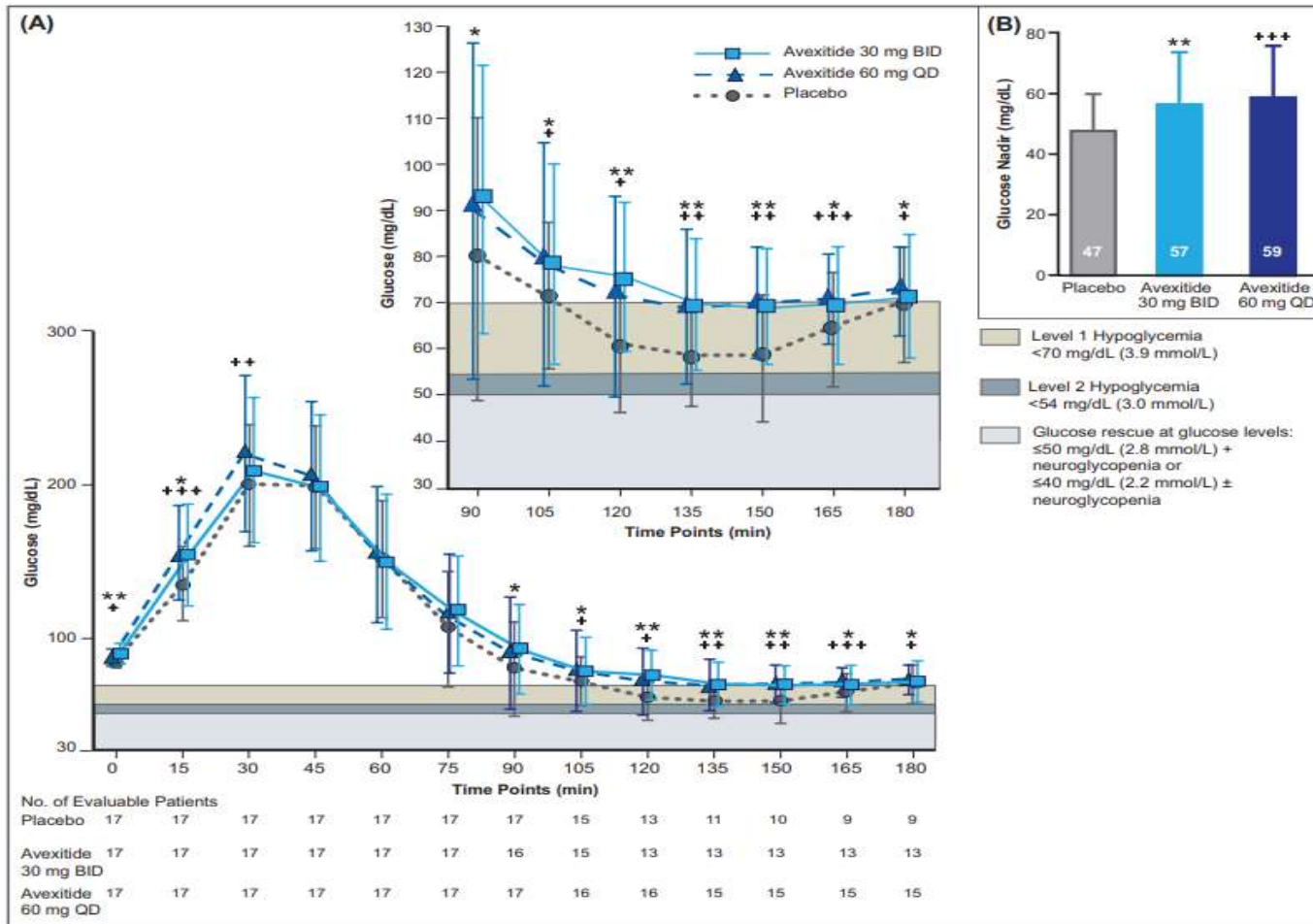
- Fas 2
- GLP-1-antagonist (31 aa av Exenatid)
- RCT
- n18

AVEXITIDE



PREVENT: A Randomized, Placebo-controlled Crossover Trial of Avexitide for Treatment of Postbariatric Hypoglycemia

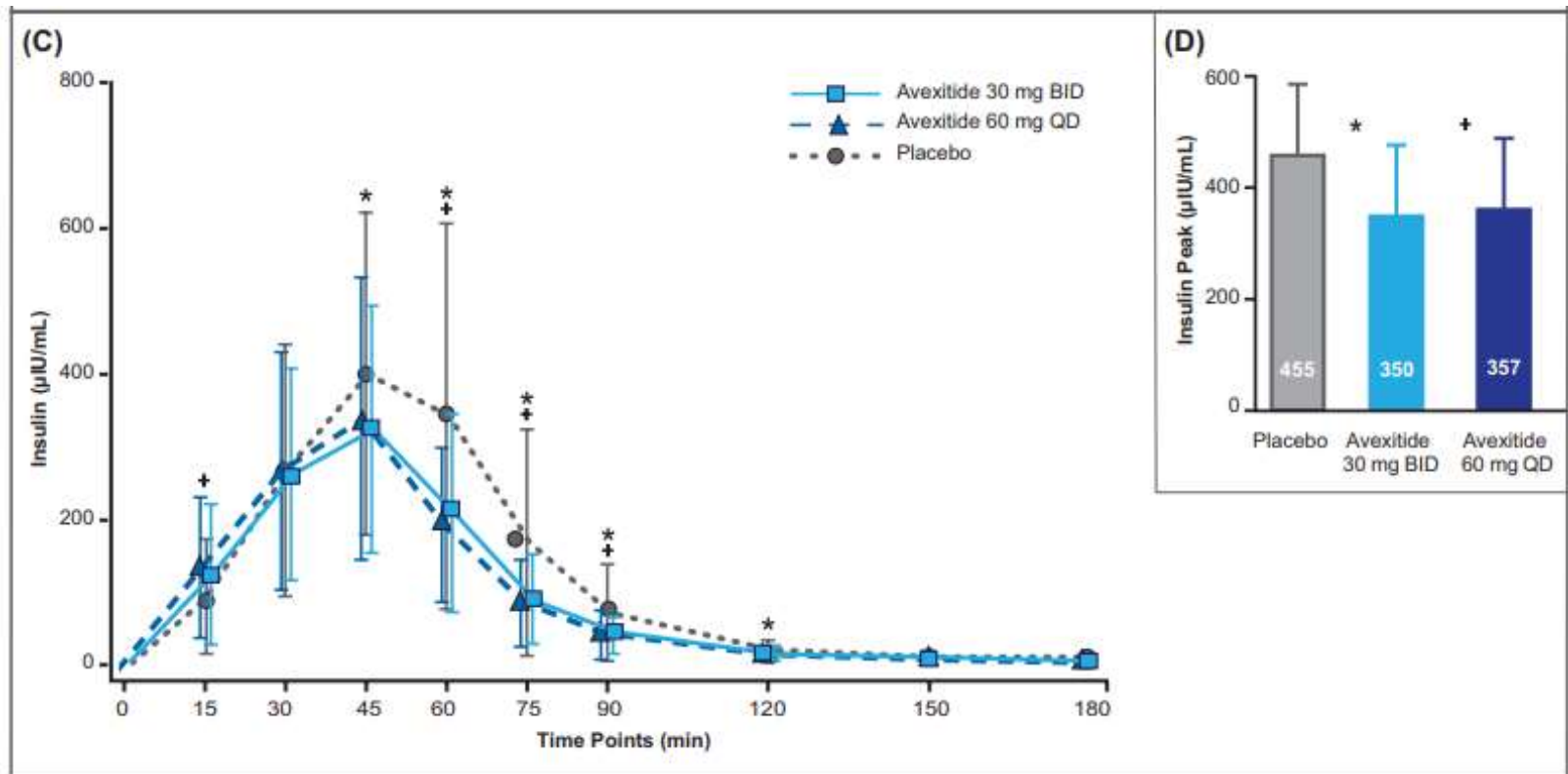
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Table 4. Treatment-emergent adverse events reported in $\geq 10\%$ of patients overall

Preferred term	Number (%) of patients			
	Treatment			Overall (N = 18)
	Placebo (N = 18)	Avexitide 30 mg twice daily (N = 18)	Avexitide 60 mg once daily (N = 18)	
All TEAEs	14 (77.8)	7 (38.9)	13 (72.2)	16 (88.9)
Injection site bruising	7 (38.9)	0	1 (5.6)	7 (38.9)
Headache	4 (22.2)	1 (5.6)	1 (5.6)	5 (27.8)
Nausea	4 (22.2)	2 (11.1)	3 (16.7)	4 (22.2)
Dizziness	1 (5.6)	0	1 (5.6)	2 (11.1)
Injection site pain	1 (5.6)	0	1 (5.6)	2 (11.1)
Migraine	0	0	2 (11.1)	2 (11.1)

- Fas 2
- GLP-1-antagonist
- RCT
- n18

Surgical Treatment for Postprandial Hypoglycemia After Roux-en-Y Gastric Bypass: a Literature Review

- Reversal: 13 artiklar, 42 av 48 pat (88%) blev bra
- Pancreatectomy: 12 artiklar, 27 av 50 pat (54%) blev bättre

Postprandiell Normoglykem Hypokalemi

Nadir Kalium 2,1: 2,7: 2,9 för de 3 patienterna, med ackompanjerande symtom

