Cardiology Update

Davos, Switzerland, 8-12 February 2015

Bariatric surgery in obesity and type 2 diabetes

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I will not discuss off label use and/or investigational use in my presentation
I do not have financial relationship to disclose

The problem

Obesity and type 2 diabetes are epidemic

Flegal KM et al. JAMA. 2013;309:71-82

anti-obesity medications offer 5-10% body weight loss

Bray GA. *J.Clin.Endocrinol.Metab*. 2008;93:S81-S88

Lifestyle interventions deliver on average a 7% body weight loss

Bray GA. *J.Clin.Endocrinol.Metab*. 2008;93:S81-S88

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The problem

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

N Engl J Med 2013;369:145-54.

Cardiovascular events in overweight or obese with type 2 diabetes were not reduced over a maximum follow-up of 13.5 years

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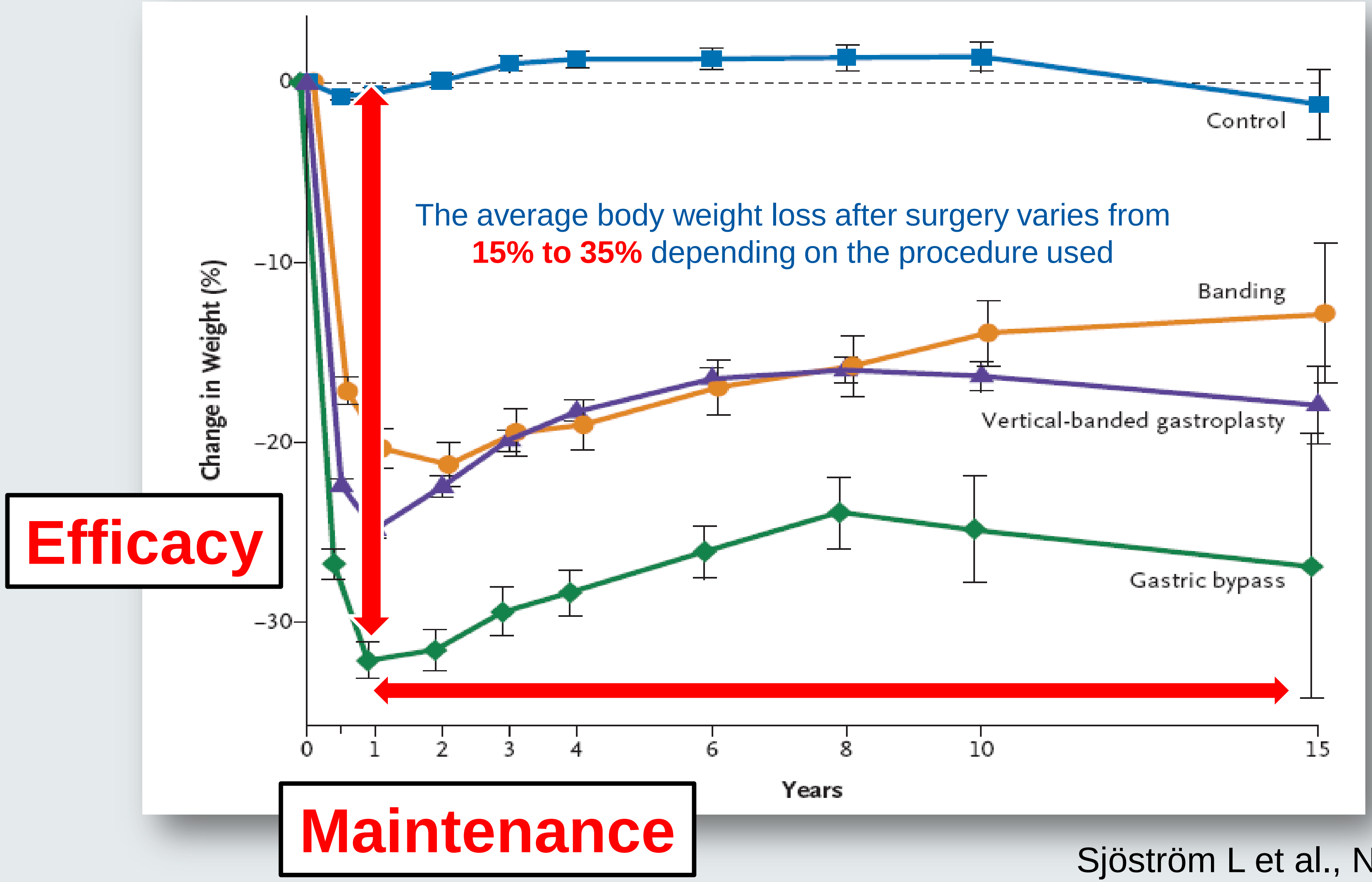
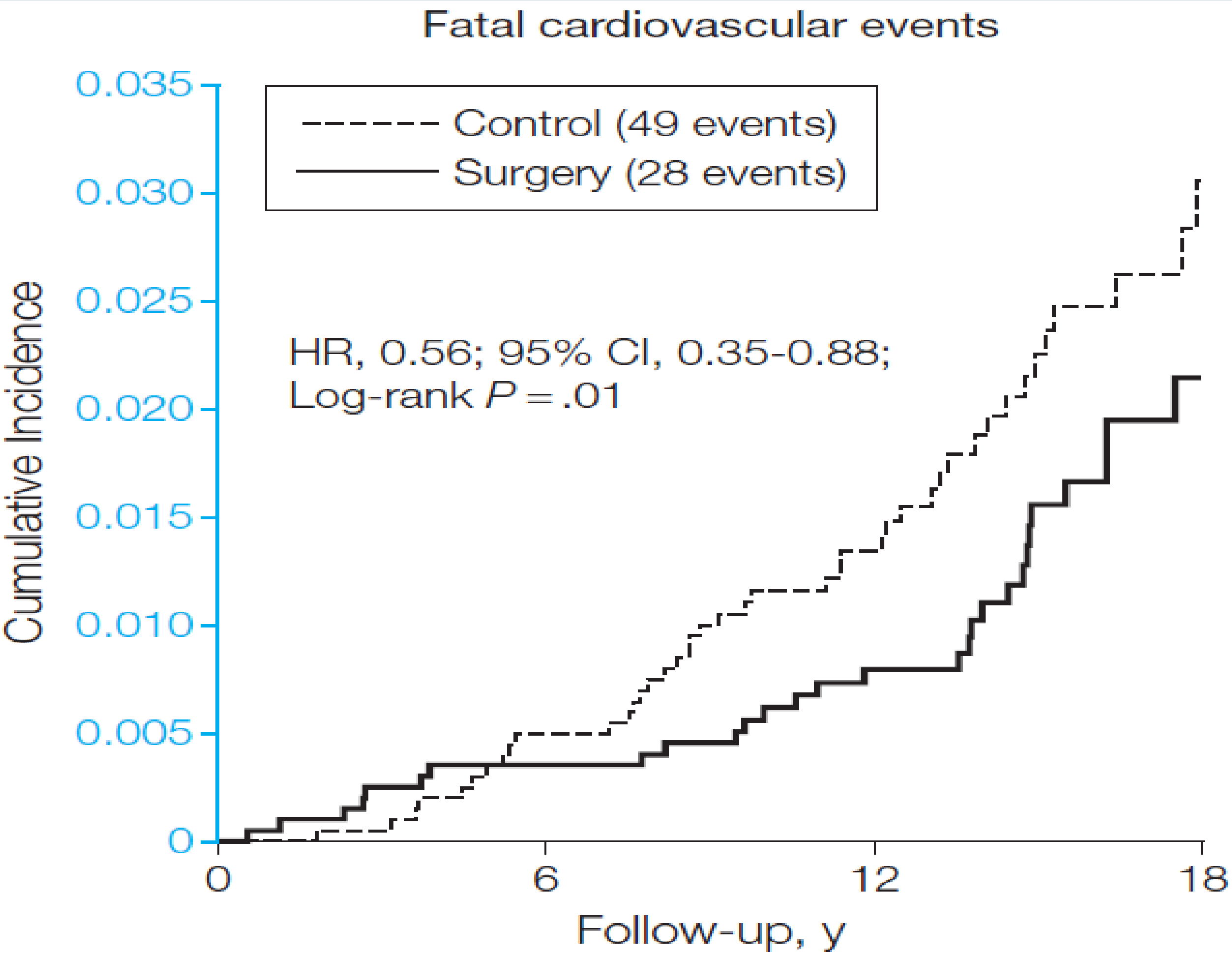
Swedish Obese Subjects (SOS) study



Sjöström L et al., NEJM 2004

Bariatric surgery reduces cardiovascular morbidity and mortality



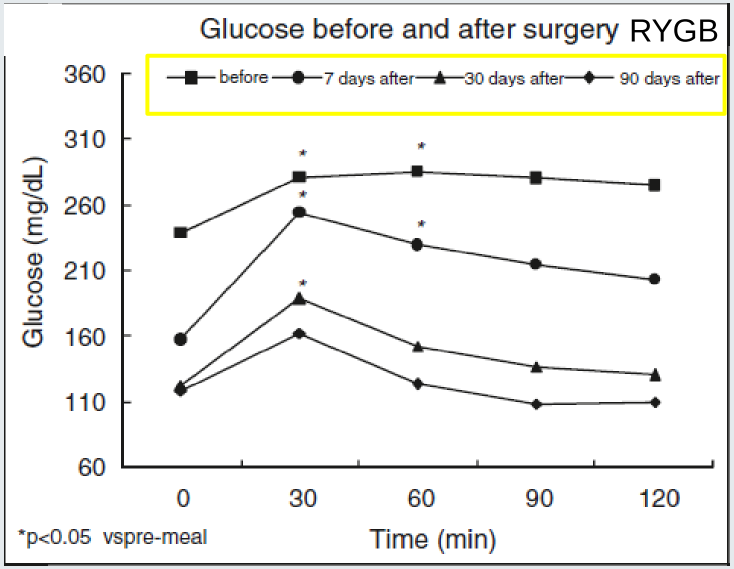
Sjöström et al JAMA 2012

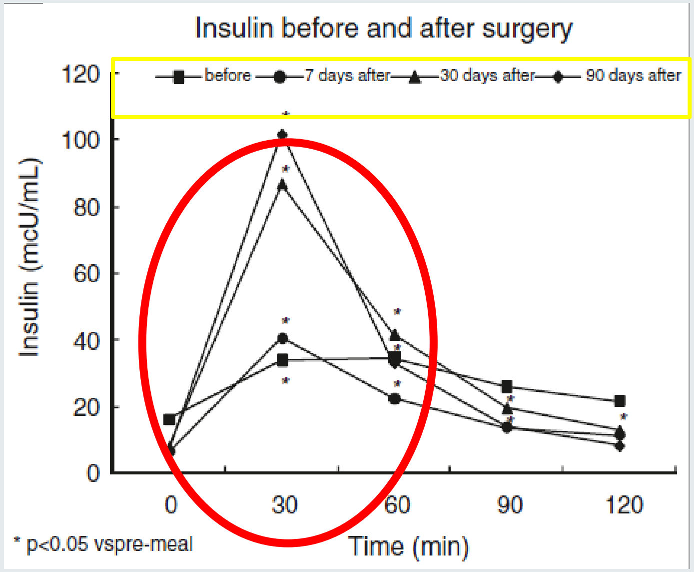
the magnitude of the cardiovascular risk factors reduction in the short to medium term after bariatric surgery exceeds the effect of weight loss itself

Vest AR et al Circulation. 2013

Metabolic surgery

Glycemia, insulin secretion and sensitivity is restored immediately after bariatric surgery, before any significant body weight loss





Umeda LM et al., Obes Surg 2011

Pournaras D et al, Ann Surg 2010

Randomized controlled evidence

ORIGINAL ARTICLE

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

Philip R. Schauer, M.D., Deepak L. Bhatt, M.D., M.P.H., John P. Kirwan, Ph.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., Sankar D. Navaneethan, M.D., M.P.H., Ali Aminian, M.D., Claire E. Pothier, M.P.H., Esther S.H. Kim, M.D., M.P.H., Steven E. Nissen, M.D., and Sangeeta R. Kashyap, M.D., for the STAMPEDE Investigators*

N Engl J Med 2014;370:2002-13.

JAMA. 2013;309(21):2240-2249

Roux-en-Y Gastric Bypass vs Intensive Medical Management for the Control of Type 2 Diabetes, Hypertension, and Hyperlipidemia

The Diabetes Surgery Study Randomized Clinical Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

Geltrude Mingrone, M.D., Simona Panunzi, Ph.D., Andrea De Gaetano, M.D., Ph.D., Caterina Guidone, M.D., Amerigo Iaconelli, M.D., Laura Leccesi, M.D., Giuseppe Nanni, M.D., Alfons Pomp, M.D., Marco Castagneto, M.D., Giovanni Ghirlanda, M.D., and Francesco Rubino, M.D.

At 2 years, diabetes remission in no patients on medical-therapy versus 75% after gastric-bypass and 95% in the biliopancreatic-diversiongroup

type 2 diabetes mellitus improves through various mechanisms beyond reduced food intake and body weight loss

Rubino et al. Annu. Rev. Med. 2010

Who Would Have Thought It?

An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus

Pories W et al., Ann Surg 1995

From a gastrointestinal operation that was designed to promote only weight loss to

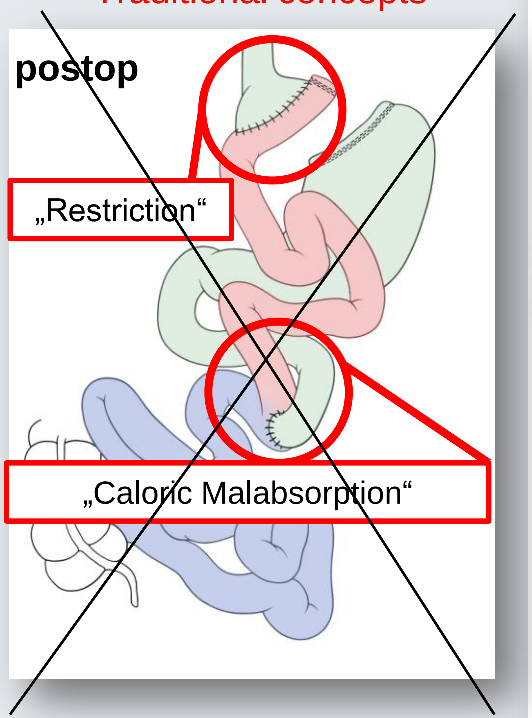
Metabolic surgery

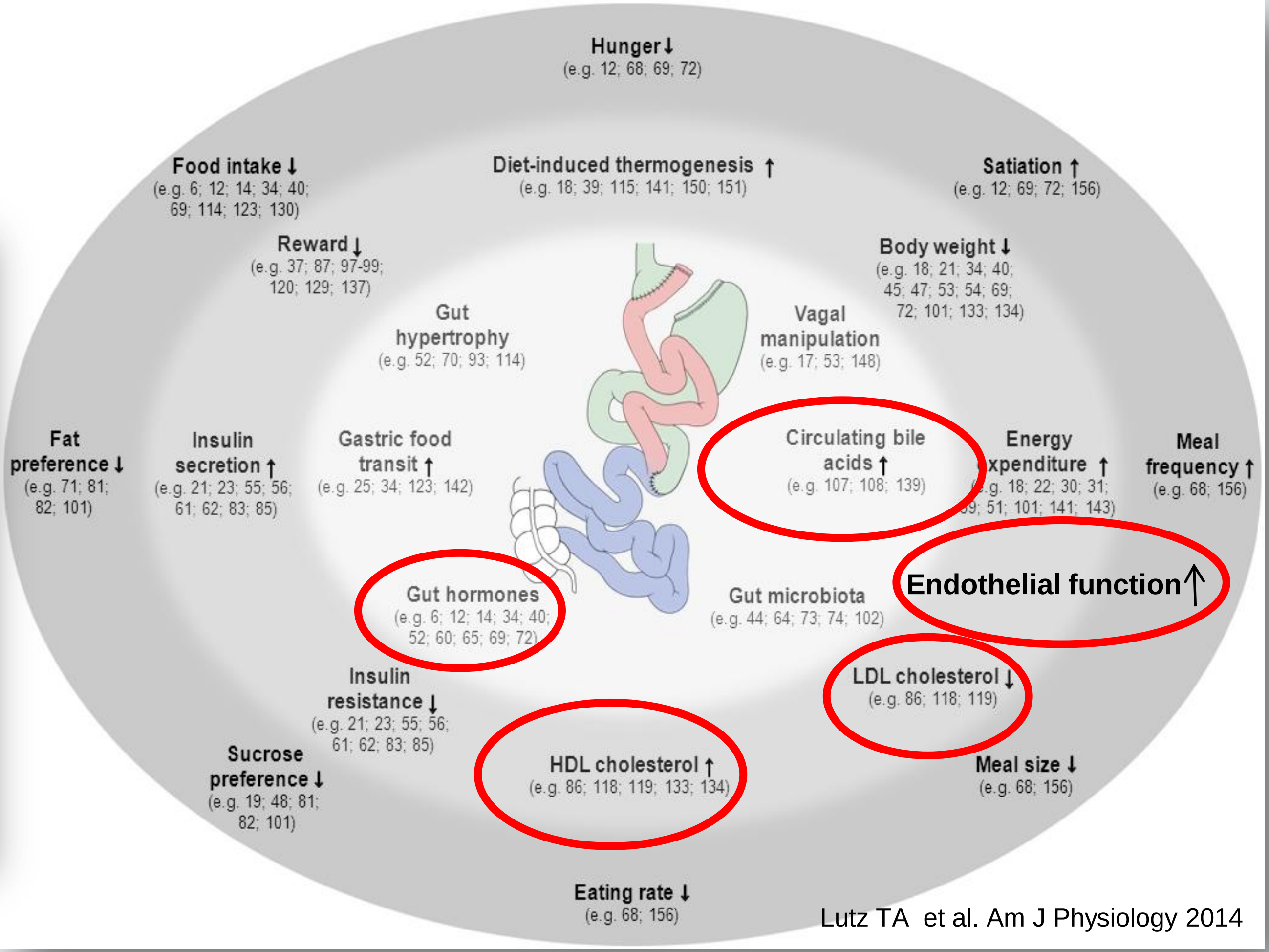
Rubino et al. Annu. Rev. Med. 2010

Mechanisms

how does this work? Why is bariatric surgery, in particular RYGB, superior to other weight loss strategies?

Traditional concepts



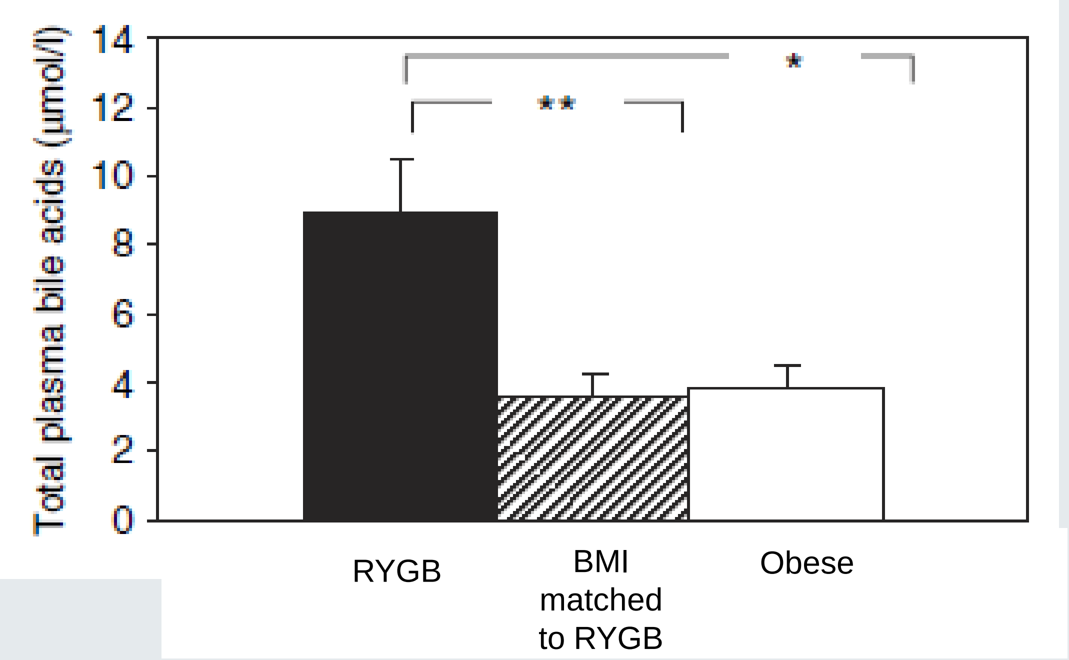


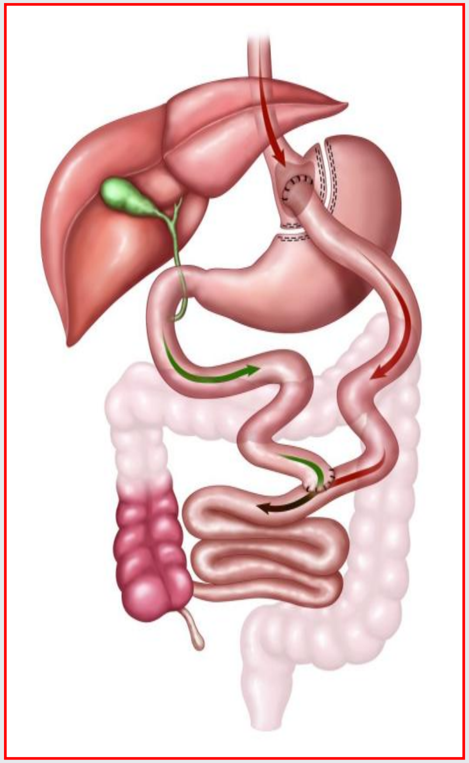
Lutz TA et al. Am J Physiology 2014

The beneficial effects likely derive from the unique anatomical gut re-arrangement and the altered flow of nutrients after RYGB rather than simply from weight loss

Mechanisms

After RYGB, the modified entero-hepatic circulation of bile acids increases their intraluminal and systemic concentrations.





Patti MA et al. Obesity 2009

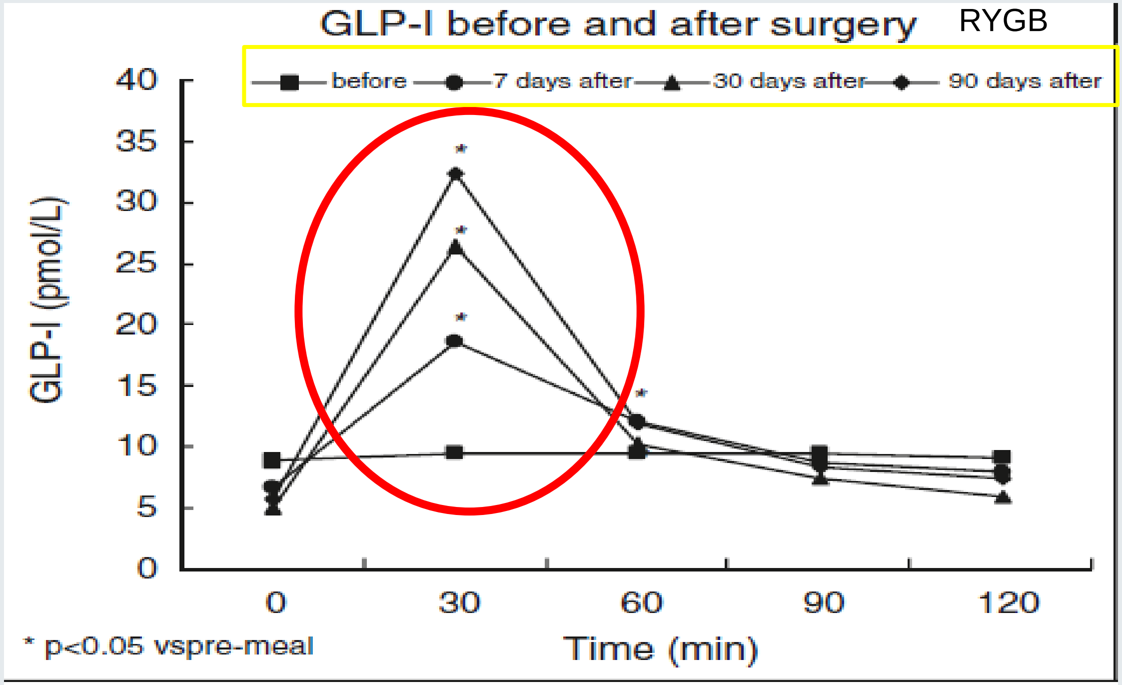
elevated levels of bile acids may modify the release of gastrointestinal hormones and in particular Glucagon like peptide 1

Mechanisms

plasma fasting and postprandial levels of GLP-1 increase rapidly after RYGB,

Umeda LM et al., Obes Surg 2011

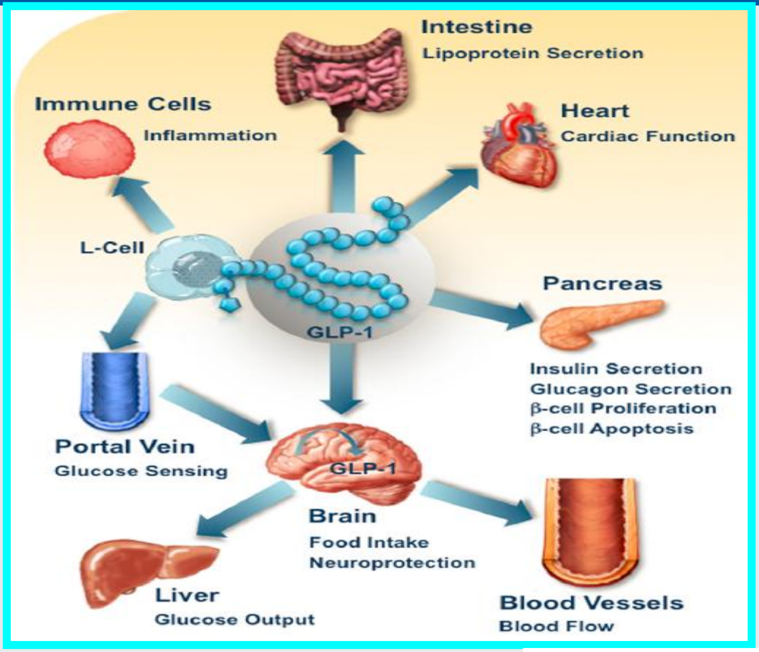
Jørgensen NB et al Diabetes 62:3044–3052, 2013



but not after dietary restriction, despite a similar weight loss

***Laferrere B et al J Clin Endocrinol Metab* 2008**

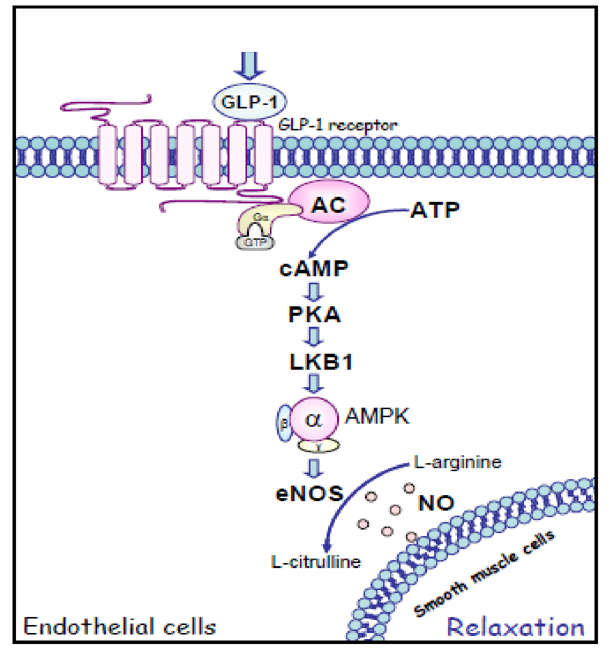
Mechanisms



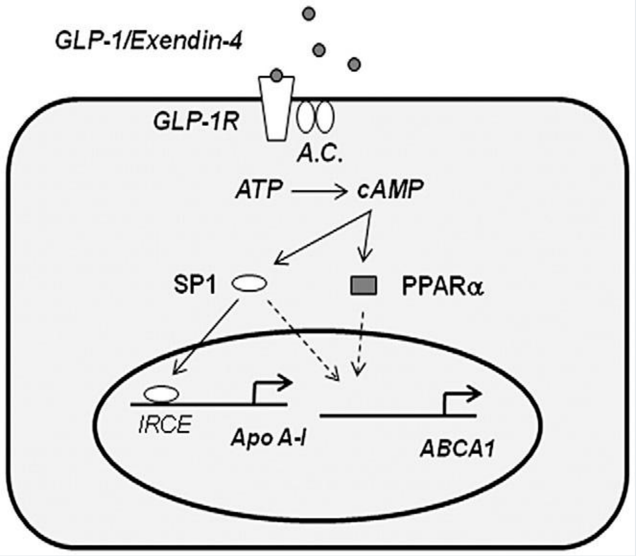
glucagon-like peptide (GLP1) has pleiotropic cardio-metabolic actions

Campbell, J. et al Cell Metabolism. 2013

endothelial vasorelaxation



HDL synthesis and efflux



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Aim

to investigate the rapid effects

of RYGB on obesity-induced

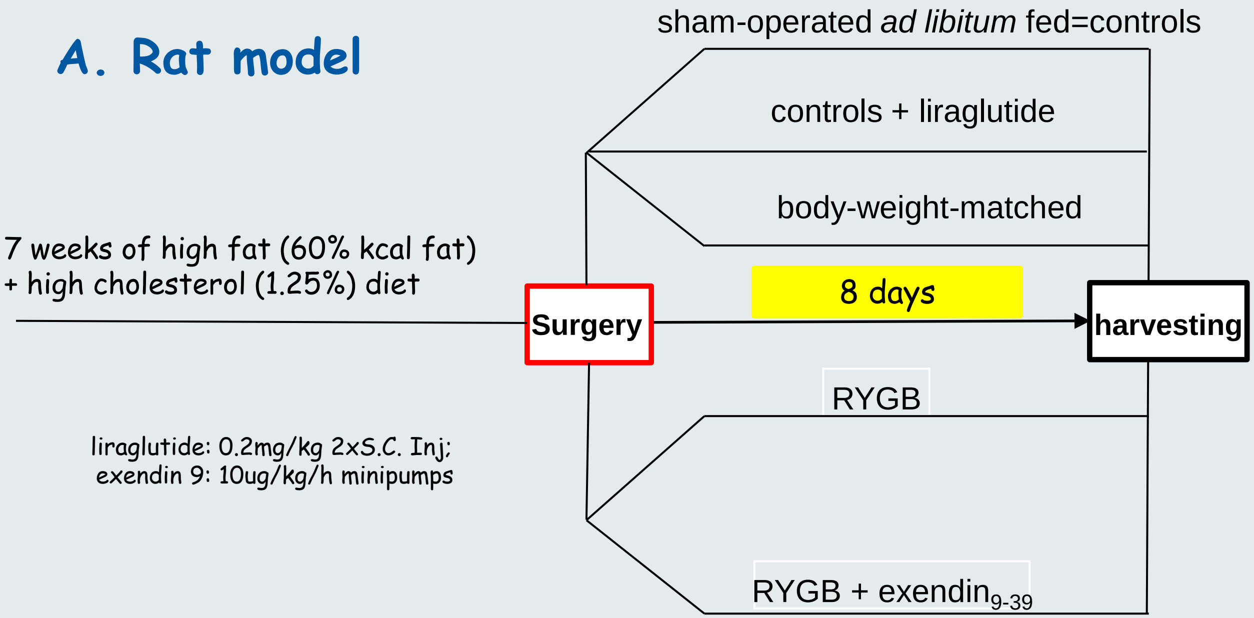
endothelial and HDL dysfunction

and whether GLP-1 has a role in these effects

Study design

Osto E et al. Circulation 2015

A. Rat model

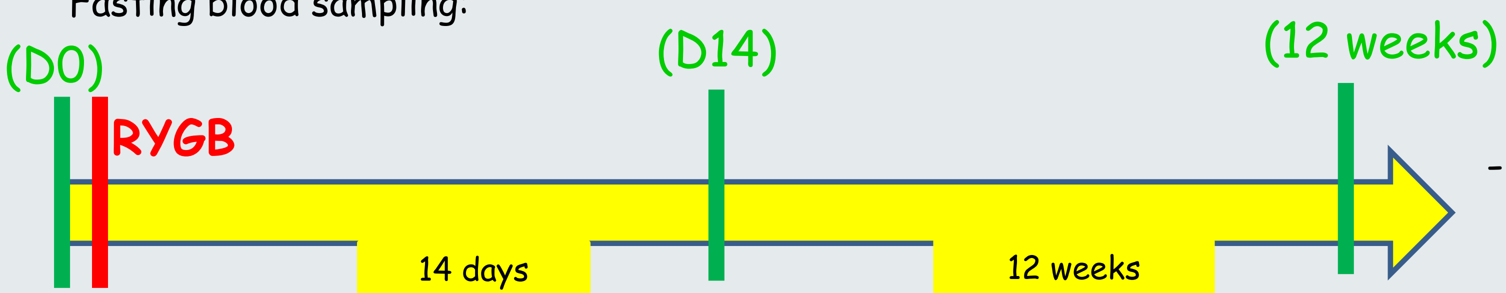


-endothelial function

-HDL properties evaluation

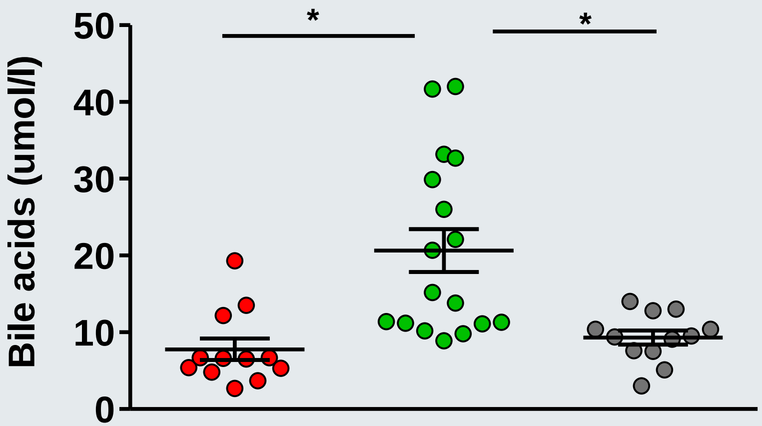
B. 29 Patients-28 Healthy -29 BMI-matched to 12weeks

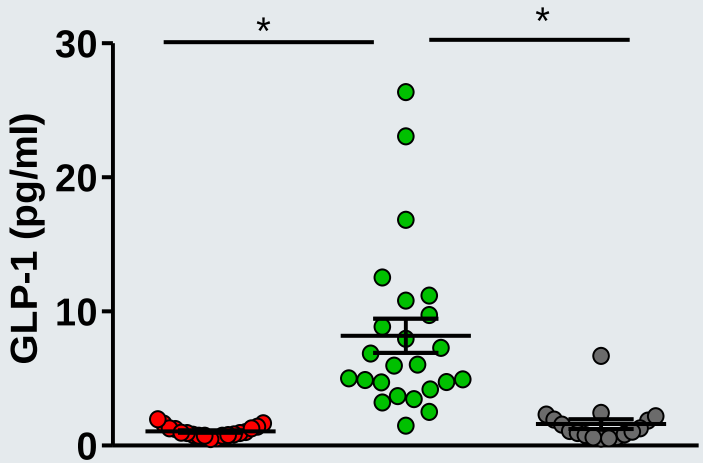
Fasting blood sampling:



-HDL properties evaluation

Results





	RYGB D0	RYGB D14 (n=29)	RYGB 12W	BMI-matched to 12W RYGB (n=29)	Healthy (n =28)
GLP-1, pg/ml	0.70±0.11	3.88±0.49[b]	2.3±0.42[b]		1.5±1.9
Bile acids,umol/L	8.23±0.49[a]	9.40±0.53[a]	11.79±0.75[bc]		12.09±0.73
Glucose, mmol/L	6.40±0.25[a]	5.39±0.11[b]	5.12±0.11[b]	5.49±0.27	5.29±0.15
Insulin, u UI/ml	19.91±2.87[a]	13.49±1.48[ab]	11.60±1.48[b]	13.91±1.64	6.18±1.0
HOMA IR	2.62±0.34[a]	1.81±0.16[ab]	1.44±0.16[bc]	1.81±0.21	0.82±0.14

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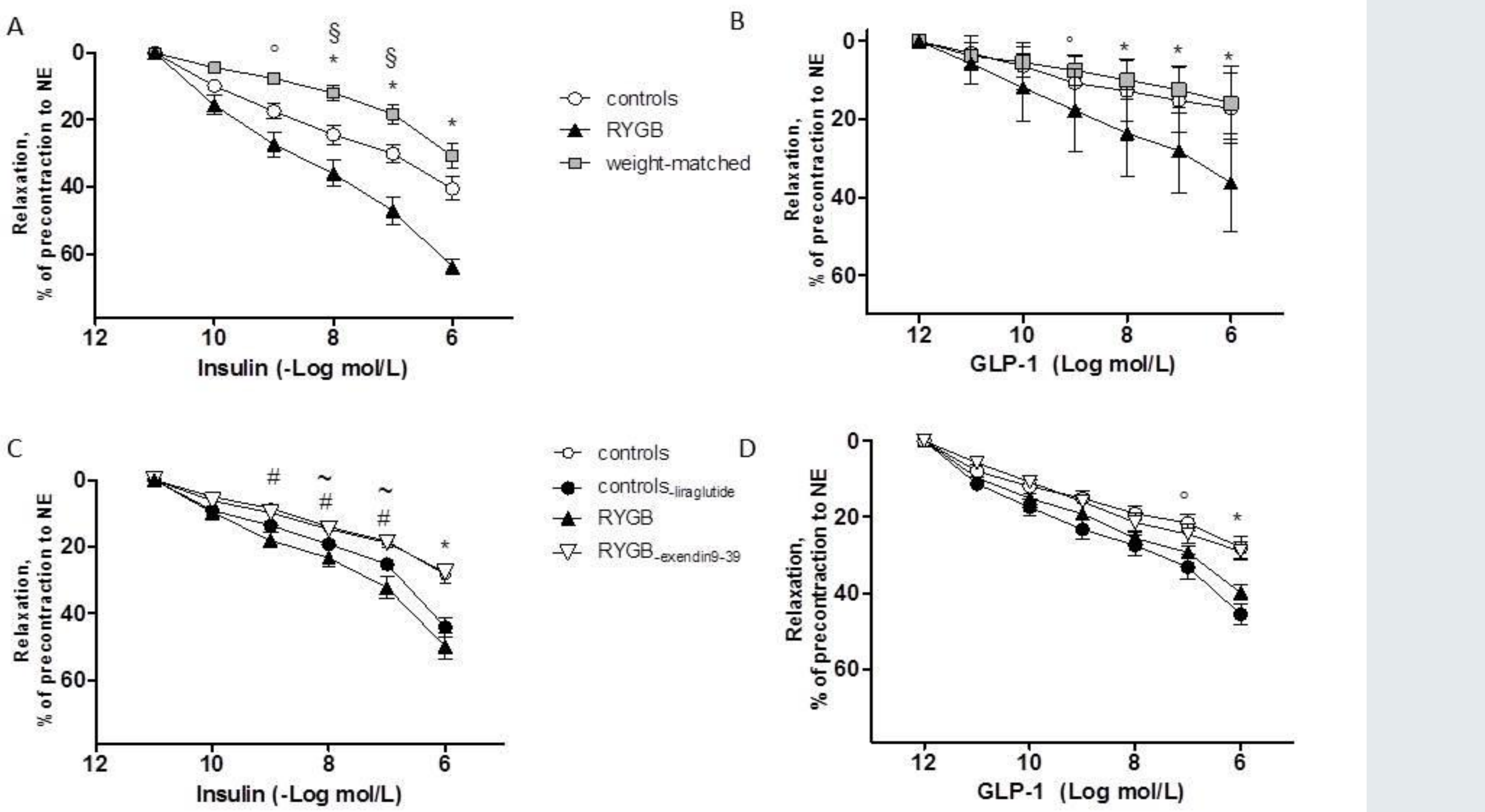
Endothelial vasorelaxation



Pre-incubation with L-NAME completely inhibited the relaxation induced by both insulin and GLP-1

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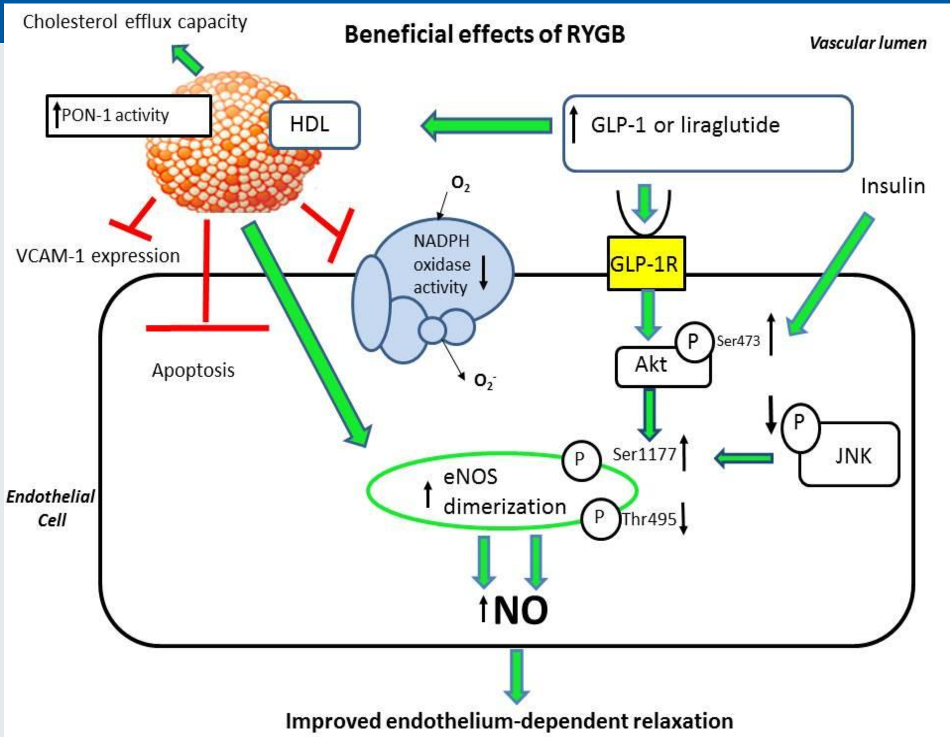

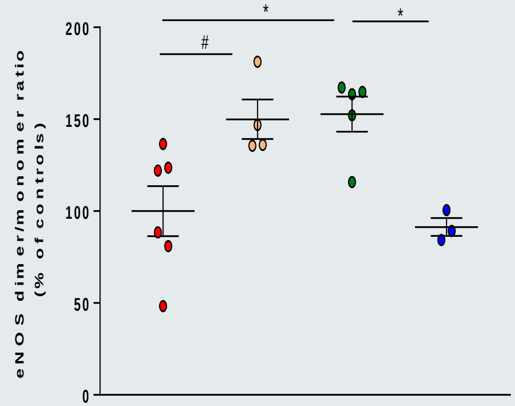

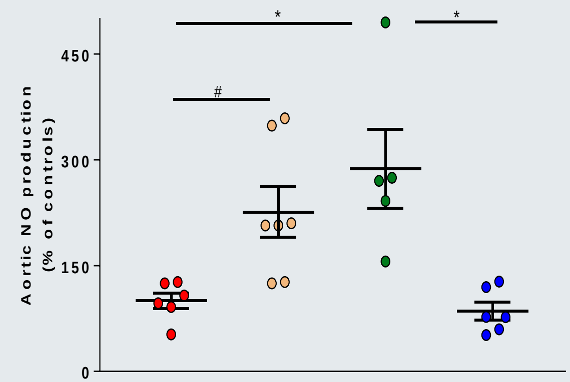

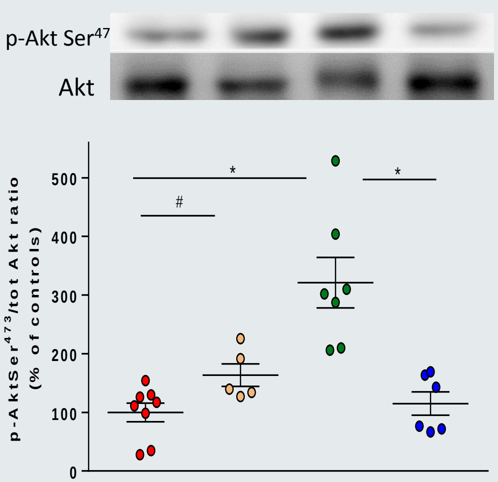

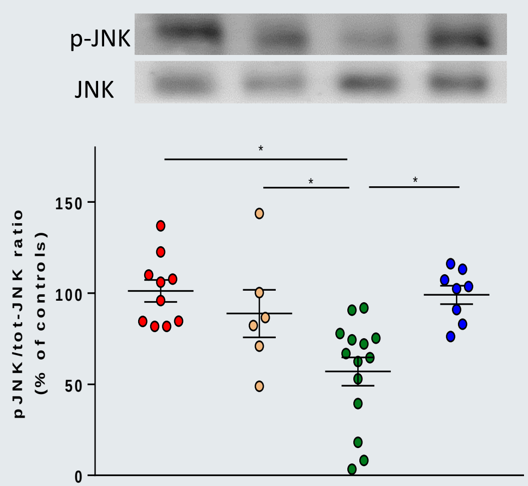

In obese rat, RYGB rapidly

(1) reduced oxidative stress, increased aortic NO bioavailability

(2) GLP-1-dependent signaling was selectively activated in rat aortae after RYGB independently from weight loss and was mimicked by liraglutide treatment

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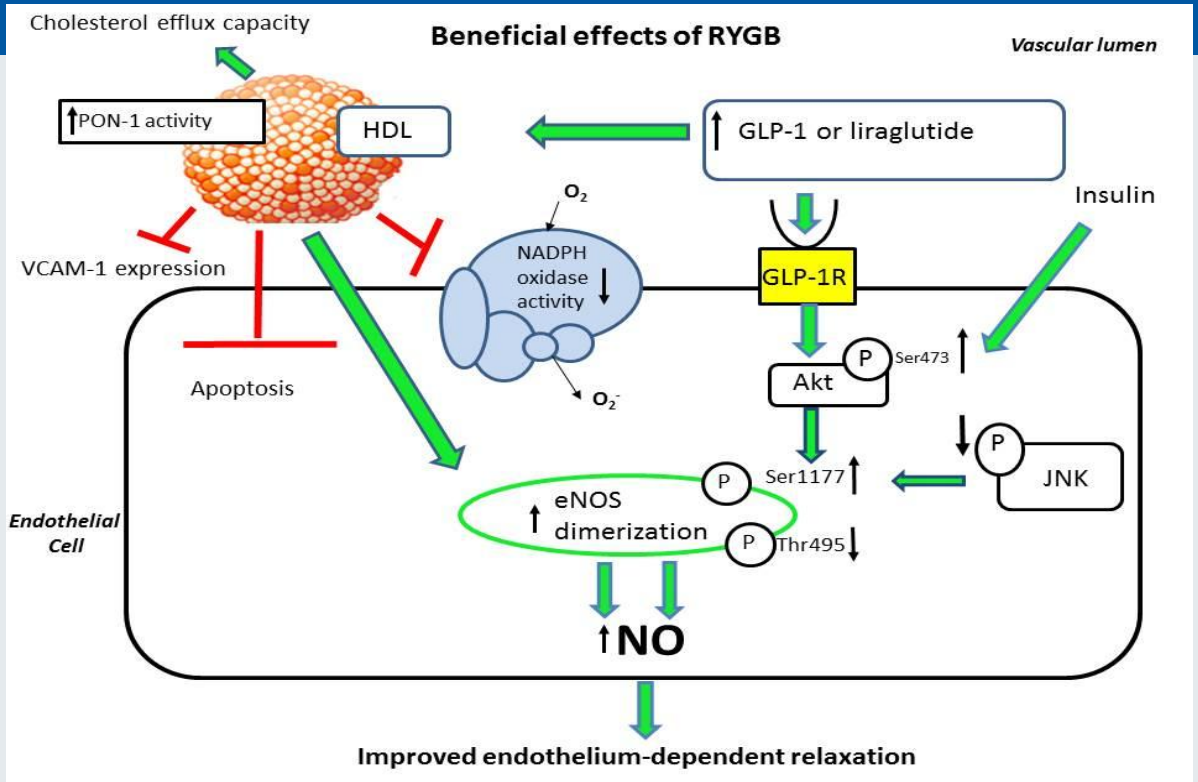
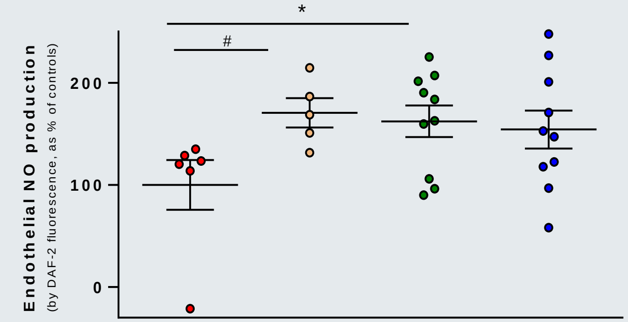
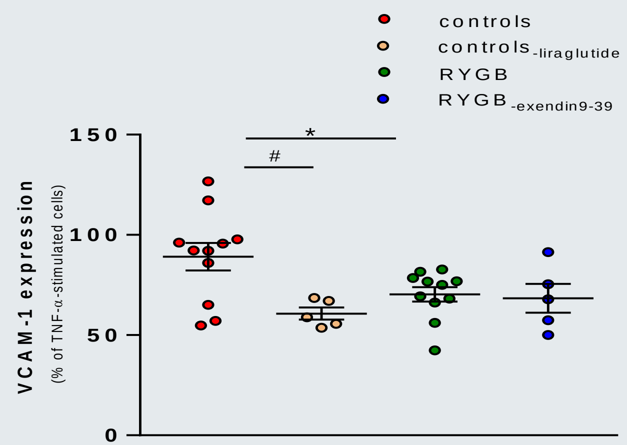
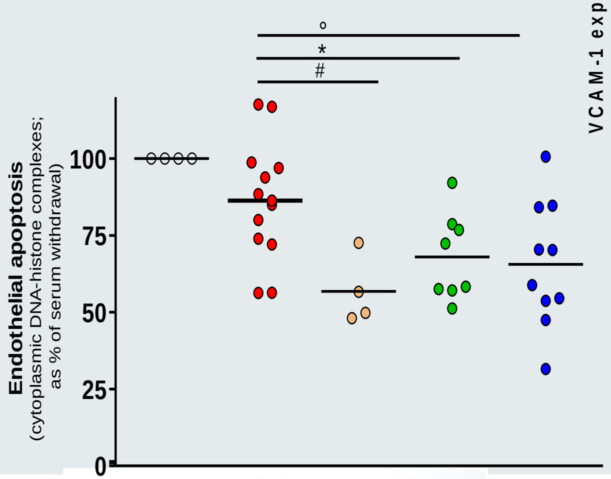






In obese rat, RYGB rapidly improved endothelial protective properties of HDL



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Clinical Characteristics in patients and healthy subjects

	RYGB D0	RYGB D14 (n=29)	RYGB 12W	BMI-matched to 12W RYGB (n=29)	Healthy (n =28)
Age, years	40.9 ± 1.7			42.7±2.1	37.8±2.4
Female gender, n (%)	17 (58.6%)			19 (65%)	14 (50%)
Height, m	1.7 ± 0.01			1.7 ± 0.01	1.7 ± 0.01
Body weight, kg	134.0 ± 3.7[a]	124.0 ± 3.4[b]	109.3 ± 3.4[ac]	110.3 ± 3.8	66.0 ± 1.8
BMI (kg/m^2)	45.4 ± 1.0[a]	42.2 ± 1.0[b]	37.0 ± 1.0[abc]	37.15 ± 0.9	21.9 ± 0.3
Current smokers (%)	5/29 (17%)	4/29 (14%)	3/29 (10%)	5/29 (17%)	
Diabetes, n (%)	6/29 (20.7%)	4/29 (13.8%)	0/29b (0%)	2/29 (6.9%)	
OSAS	9/29 (31.0%)	7/29 (24.1%)	6/29 (20.7%)	10/29(34.5%)	
Lipid profile					
Total cholesterol (mmol/l)	4.8 ± 0.2	4.2 ± 0.2[ab]	4.0 ± 0.1[ab]	5.10 ± 0.20	4.89 ± 0.10
LDL (mmol/l)	3.0 ± 0.1	2.6 ± 0.1[b]	2.4 ± 0.1[b]	309 ± 0.19	2.8 ± 0.16
HDL (mmol/l)	1.0 ± 0.1[a]	0.8 ± 0.05[ab]	1.0 ± 0.1[ac]	1.19 ± 0.04	1.62 ± 0.10
LDL/HDL	3.14 ± 0.23[a]	3.35 ± 0.24[a]	2.70 ± 0.16[abc]	2.65 ± 0.19	1.87 ± 0.19
TG (mmol/l)	1.72 ± 0.13[a]	1.80 ± 0.12[a]	1.45 ± 0.06[ac]	2.47 ± 0.29	0.95 ± 0.08
Medications					
Metformin, n (%)	3/29 (10.3%)	2/29 (6.9%)	0/29 (0%)	2/29 (6.9%)	
ACEI (%)	2/29 (6.9%)	2/29 (6.9%)	0/29 (0%)	1/29 (3.4%)	
Sartans	2/29 (6.9%)	2/29 (6.9%)	2/29 (6.9%)	0/29	
B-blockers	5/29 (17.2%)	5/29 (17.2%)	1/29 (3.4%)	0/29	
Statins	0/29 (0%)	0/29 (0%)	0/29 (0%)	6/29 (20.7%)	
Ca-channels blockers	2/29 (6.9%)	2/29 (6.9%)	1/29 (3.4%)	0/29	
Diuretics	3/29 (10.3%)	2/29 (6.9%)	1/29 (3.4%)	1/29 (3.4%)	
Others (Gliptins)	1/29 (3.4%)	1/29 (3.4%)	0/29 (0%)	0/29	

values are mean ± SE. Letters indicate statistically significant difference from : (a) healthy, (b) D0, (c) D14; $p<0.05$. BMI, body mass index. OSAS, obstructive sleep apnea syndrome. LDL, low density lipoprotein. HDL, high density lipoprotein. TG, triglycerides. ACEI, Angiotensin-converting-enzyme inhibitors.

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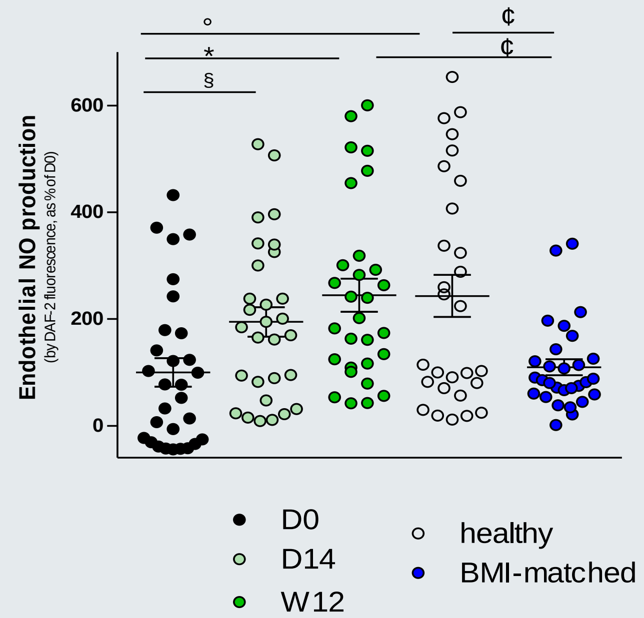
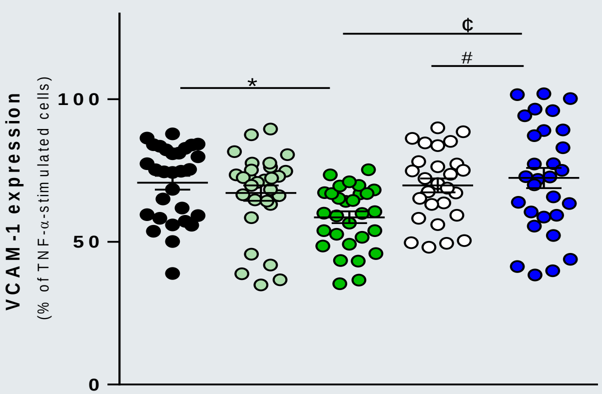
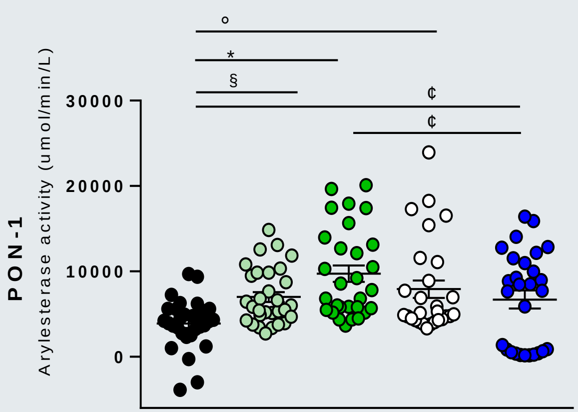
HDL properties in Patients

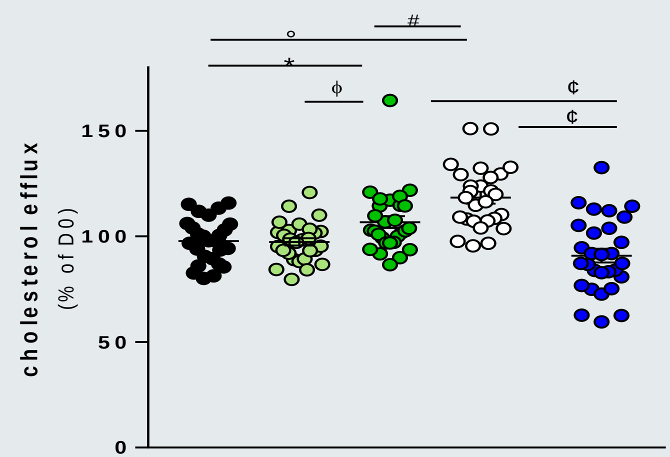
HDL properties improved 12 weeks after RYGB to the level of healthy subjects, although the patients were still obese. Instead, HDL properties were impaired in BMI-matched patients.

degree of weight and BMI loss induced by surgery is not sufficient or critical per se to improve the protective properties of HDL









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Conclusion

The superior benefits of bariatric surgery compared to current conservative management likely result from the influence of surgery on several cardio-metabolic aspects. Some of these may be GLP-1 mediated.

Understanding how bariatric surgery leads to these cardio-metabolic benefits may help to design novel therapeutic strategies against morbid obesity and in particular its severe cardiovascular risk.

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Bariatric surgery reverses end organ damage Mingrone et al D