

# Incontro Congiunto SICOb – SID – SIO 2014

Con il patrocinio di



PADOVA, 7/8 marzo

Aula Magna,  
Dipartimento Militare  
di Medicina Legale  
Ex Ospedale Militare

## Simposio 2.

Recidive del diabete dopo terapia chirurgica

**Soluzioni: Terapia farmacologica**

Maria Grazia Zenti

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# Background

- La chirurgia bariatrica consente di ottenere risultati duraturi nel trattamento dell'obesità, con un significativo miglioramento del controllo glicemico, dell'insulino-resistenza, della funzione beta-cellulare e, in molti casi, con remissione del diabete
- Il “Time course” della remissione del diabete dopo chirurgia bariatrica è molto variabile (pochi giorni, alcuni mesi, anni)
- Non esiste un algoritmo validato per il trattamento dei pazienti diabetici dopo chirurgia bariatrica



ELSEVIER

Surgery for Obesity and Related Diseases 9 (2013) 159–191

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SURGERY FOR OBESITY  
AND RELATED DISEASES

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AACE/TOS/ASMBS Guidelines

Clinical Practice Guidelines for the Perioperative Nutritional, Metabolic,  
and Nonsurgical Support of the Bariatric Surgery Patient—2013 Update:  
Cosponsored by American Association of Clinical Endocrinologists,  
The Obesity Society, and American Society for Metabolic  
& Bariatric Surgery<sup>☆</sup>

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**R36(58–61)-r.** In patients with diabetes, the use of all insulin secretagogues (sulfonylureas and meglitinides) should be discontinued and insulin doses should be adjusted postoperatively (due to low calorie intake) to minimize the risk for hypoglycemia (**Grade D**). Antidiabetic medications should be withheld if the T2D is in remission following bariatric surgery (**Grade D**). Metformin may be continued postoperatively until prolonged clinical resolution of diabetes is demonstrated by normalized glycemic targets (including fasting and postprandial blood glucose and HbA<sub>1c</sub>). Insulin therapy, using a rapid-acting insulin analogue (insulin lispro, aspart, or glulisine) before meals and a basal long-acting insulin analogue (insulin glargine or detemir) should be used to attain glycemic targets (140–180 mg/dL) in nonintensive care unit hospitalized patients (**Grade D**). In the intensive care unit, intravenous regular insulin, as part of a standard intensive insulin therapy protocol, should be used to control hyperglycemia to a 140–180 mg/dL blood glucose target (**Grade D**). Antidiabetic medications that improve insulin sensitivity (metformin), as well as incretin-based therapies, should be considered in outpatients not reaching glycemic targets. (**Grade D**). Endocrinology consultation should be considered for patients with uncontrolled hyperglycemia (**Grade D**).

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◆ **Metformin may be continued postoperatively until prolonged clinical resolution of diabetes is demonstrated by normalized glycemic targets**

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◆ insulin therapy, using a rapid –acting insulin analogue (**lispro, aspart, glulisine**) before meals and a basal long-acting insulin analogue (**glargine, detemir**)

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◆ **incretin based therapies, should be considered in outpatients not reaching glycemic targets**

## How Do We Define Cure of Diabetes?

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### Partial remission

Hyperglycemia below diagnostic thresholds for diabetes  
(A1C <6.5%, fasting glucose 100-125 mg/dl)

At least 1 year's duration

No active pharmacologic therapy or ongoing procedures

### Complete remission

Normal glycemic measures

(A1C <6%, fasting glucose <100 mg/dl)

At least 1 year's duration

No active pharmacologic therapy or ongoing procedures

### Prolonged remission

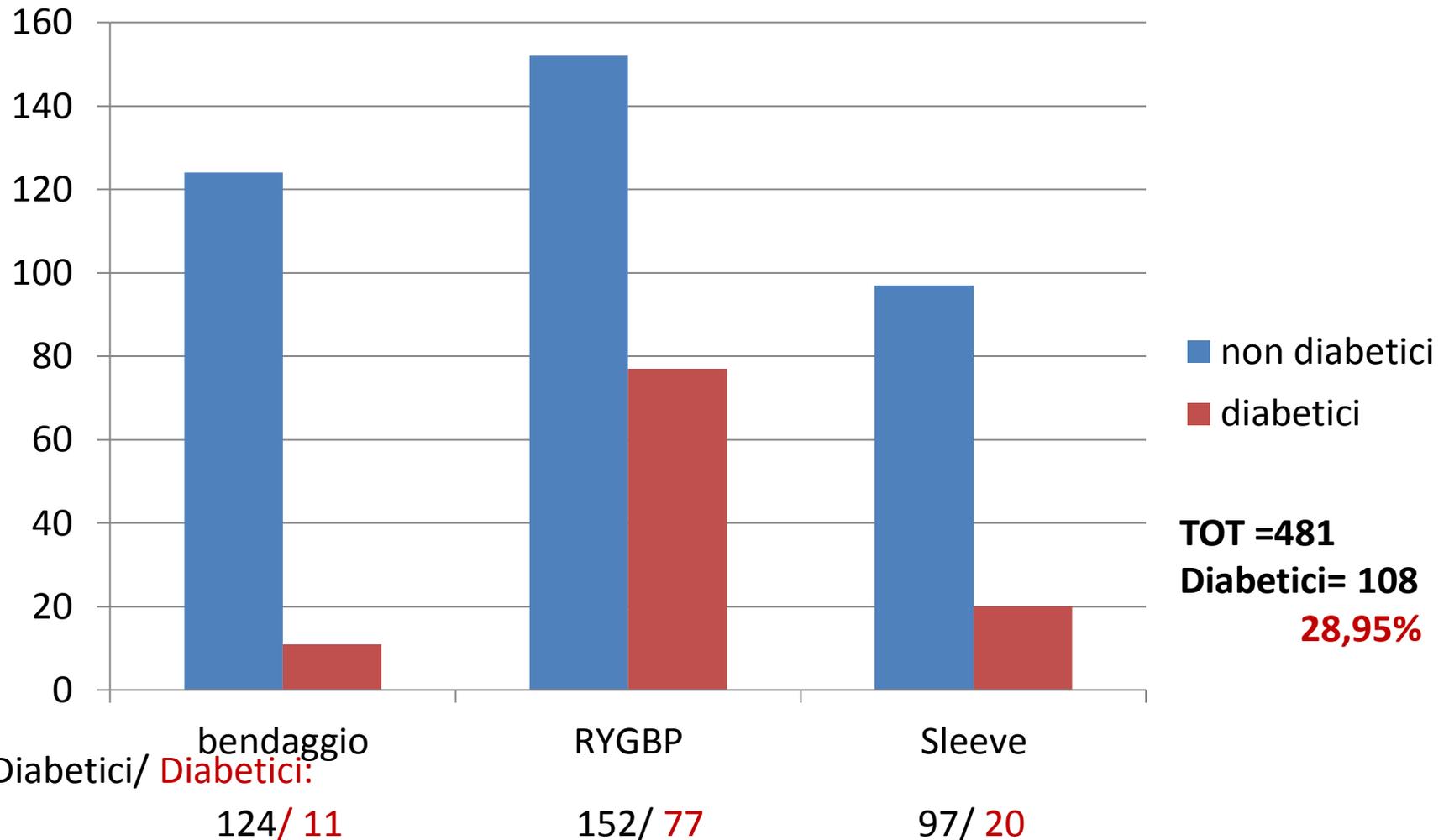
Complete remission of at least 5 year's duration



# GICOV

Gruppo Interdisciplinare  
Chirurgia Obesità Verona

## diabetici sottoposti a Chirurgia Bariatrica (2006-2013)

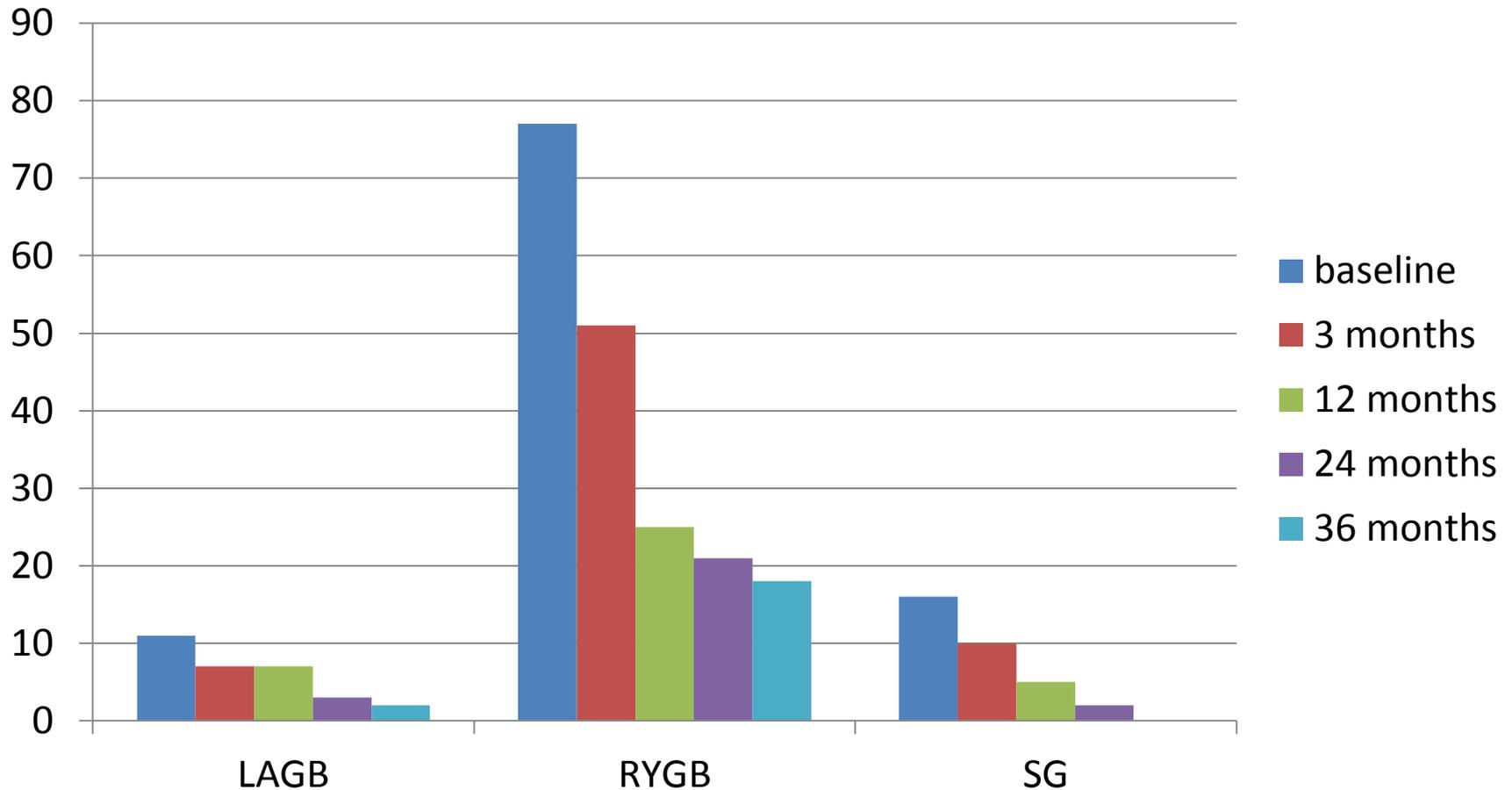




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## Diabetic patients at baseline and at 3-12-24-36 months follow-up





# GICOV

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Chirurgia Obesità Verona

## Trattamento Antidiabetico nei 104 pazienti sottoposti a chirurgia bariatrica

	base	3 mesi	6 mesi	12 mesi	24 mesi	36 mesi
n <b>diabetici</b> /n osservazioni	104/104	68/74	43/104	37/98	26/67	20/46
dieta	17	28	17	10	6	3
Antidiabetici orali	65	27	15	17	13	12
insulina	22	13	11	10	7	5

# criticità

- La gestione del diabete dopo chirurgia bariatrica è molto diversa nei diversi centri
- In molti centri viene sospesa la terapia antidiabetica, antipertensiva, ipolipemizzante, immediatamente dopo RYBP, anticipando la “cura “ delle comorbidità
- Spesso i clinici preferiscono mantenere “elevati” valori glicemici per evitare il rischi di ipoglicemia
- Uno stretto controllo glicemico dopo RYBP può migliorare gli outcomes di controllo glicemico nel lungo termine, ma espone i pazienti a rischio di ipoglicemie

## Can a Protocol for Glycaemic Control Improve Type 2 Diabetes Outcomes After Gastric Bypass?

Wiebke K. Fenske • Dimitri J. Pournaras •  
Erlend T. Aasheim • Alexander D. Miras •  
Nicola Scopinaro • Samantha Scholtz • Carel W. le Roux

### Scopo

- Stabilire algoritmo di trattamento per raggiungere un controllo glicemico ottimale in pazienti DM2 insulinotrattati, dopo RYBP
- Valutarne fattibilità, sicurezza ed efficacia

Protocol-Driven Management : n= 50

Non-Protocol-Driven Management: n=49

**Table 1** Daily insulin titration schedule in insulin-requiring type 2 diabetes after gastric bypass surgery

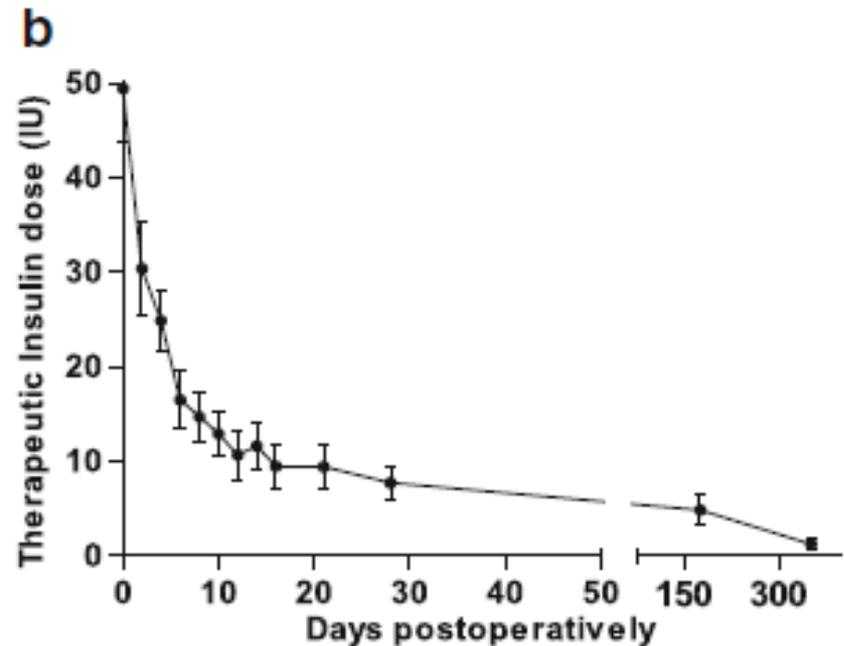
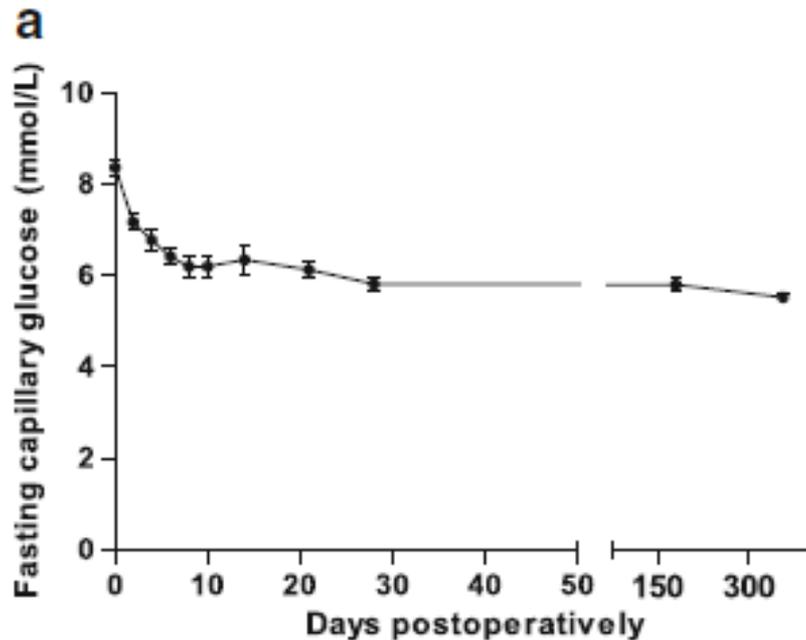
Start with dose equivalent to the insulin required in the previous 24 h prior to discharge and adjust it daily

Self-monitored fasting glucose values	Adjustment of insulin dosage (IU/day)
$\geq 12$ mmol/L (220 mg/dL)	6 $\uparrow$
$> 10$ mmol/L (180 mg/dL)	4 $\uparrow$
$> 8$ mmol/L (144 mg/dL)	2 $\uparrow$
$\geq 7$ mmol/L (120 mg/dL)	1 $\uparrow$
5.5–6.9 mmol/L (100–120 mg/dL)	No change in insulin dosage
$< 5.5$ mmol/L (100 mg/dL)	2 $\downarrow$
$< 4.5$ mmol/L (81 mg/dL)	4 $\downarrow$
$< 4.0$ mmol/L (72 mg/dL)	6 $\downarrow$

### Protocol-Driven Management:

Post-operative Care  
-Metformin 1 g twice daily (for at least 3 months, stopped when  $PG \leq 5.6$  mmol/L)  
- glargine: insulin dosage were adjusted based on a titration schedule (tab. 1)  
-Aiming for FCG levels between 5.5 and 6.9 mmol/L

# Fasting plasma glucose levels (a) and therapeutic insulin doses in units per day (b)



Greatest reduction in FG concentration occurred within the first 2 week (  $8.7 \pm 0.3$  mmol/L before  $\rightarrow$   $6.7 \pm 0.4$  mmol/L after RYBP). The mean time to reach the target FPG levels ( $<7.0$  mmol/L) was 6 days postoperatively

	Protocol-driven glycaemic control ( <i>n</i> =50)	Non-protocol-driven glycaemic control ( <i>n</i> =49)	<i>P</i> value
Baseline			
Sex, M/F	17:33	23:26	0.15
Age, years	46.7±0.9	50.7±0.9	0.1
BMI, kg/m <sup>2</sup>	47.6±0.6	47.5±0.4	0.3
HbA1c, %	9.1±0.2	8.0±0.3	0.002
Fasting glucose, mmol/L	8.7±0.3	8.5±0.5	0.7
Duration of diabetes, years	6.0±0.4	6.3±0.3	0.51
Changes at 12-month follow-up	<i>n</i> =50 (%)	<i>n</i> =49 (%)	
BMI, kg/m <sup>2</sup>	34.5±0.4	35.2±0.6	0.25
Δ HbA1C, %	-3.03±0.2	-1.2±0.3	<0.001
Δ Fasting glucose, mmol/L	-3.44±0.2	-2.0±0.5	0.02
Fasting glucose<7.0 mmol/L, <i>n</i>	47 (94.0)	33 (67.3)	<0.001
Fasting glucose<5.6 mmol/L, <i>n</i>	33 (66.0)	20 (40.8)	<0.001
HbA1C<6%, <i>n</i>	25 (50.0)	3 (6.1)	<0.001
HbA1C 6–7%, <i>n</i>	20 (40.0)	26 (53.1)	<0.05
Complete remission based on 2009 criteria [1]	25 (50.0)	3 (6.1)	<0.001
Partial remission based on 2009 criteria [1]	16 (32.0)	14 (28.6)	=0.08
Remission based on previous definition [2, 3]	41 (82.0)	17 (34.7)	<0.001

*Conclusions* The protocol-driven management proved to be feasible, safe and effective in achieving targeted glycaemic control in T2DM after RYGB. The next step will be to scrutinise the efficacy of protocol-driven management in a randomised controlled clinical trial.

# Metformina

- ◆ Rischio di acidosi lattica
- ◆ Assorbimento del farmaco dopo  
chirurgia bariatrica

# Metformin after Bariatric Surgery – an Acid Problem

Exp Clin Endocrinol Diabetes 2012; 120: 152–153

Authors

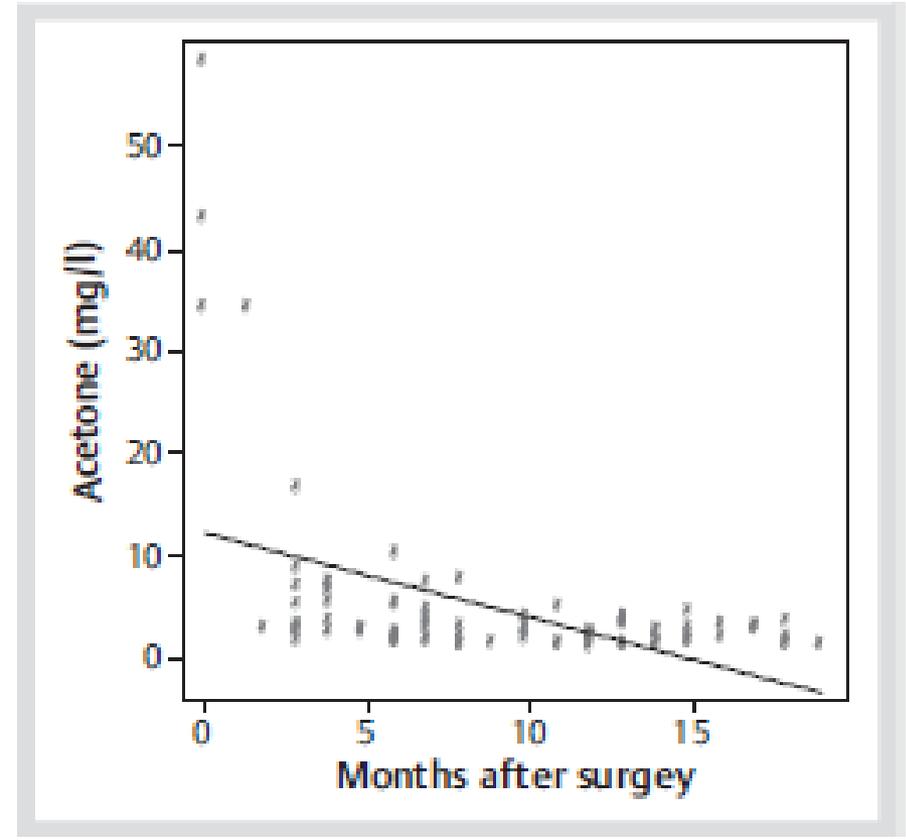
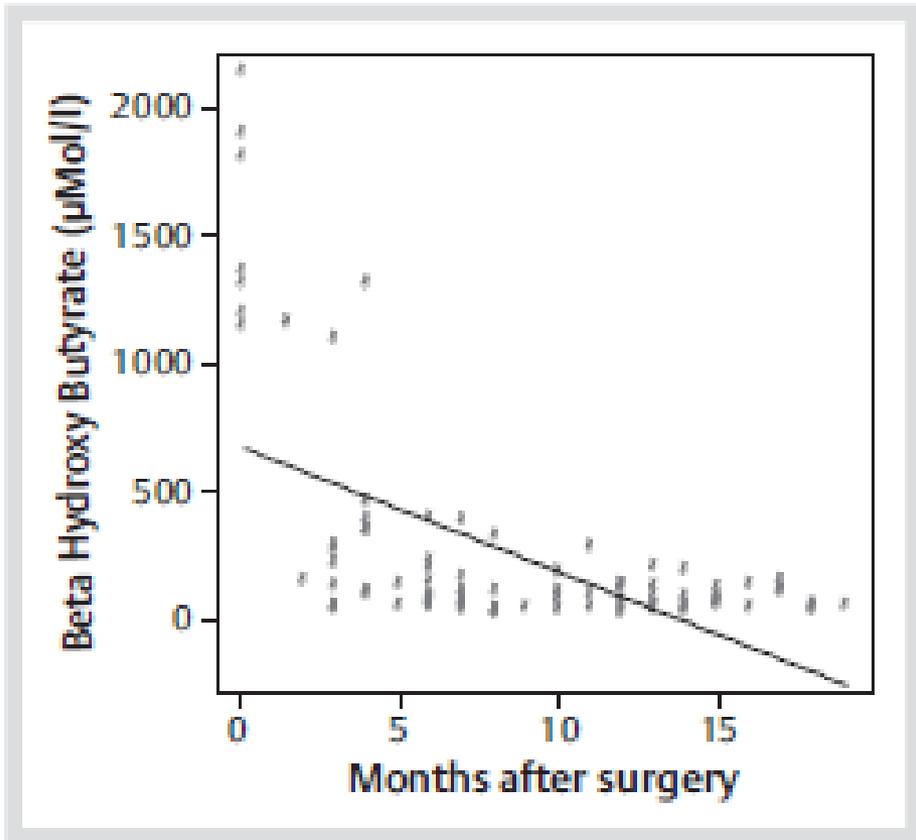
J. Aberle<sup>1</sup>, F. Reining<sup>1</sup>, V. Dannheim<sup>1</sup>, J. Flitsch<sup>1</sup>, A. Klinge<sup>2</sup>, O. Mann<sup>3</sup>

- Un gran numero di pazienti diabetici sottoposti a chirurgia bariatrica vengono trattati con metformina nel post-intervento
- Il trattamento con metformina è associato al rischio di acidosi lattica
  - Viene raccomandato di sospendere la metformina almeno 24 ore prima di qualunque procedura chirurgica e di riprendere il trattamento dopo almeno 48 ore
  - Il calo ponderale, particolarmente pronunciato nella prime settimane dopo chirurgia bariatrica, si caratterizza per una condizione di bilancio energetico negativo con formazione di **corpi chetonici** che rappresentano una condizione metabolica sfavorevole per l'uso di metformina

**Table 1** Patient characteristics and median values of ketone bodies.

n (m/f)	90 (22/68)
age (years)	45.1 ( $\pm$ 17.2)
operation	
RYGB	57
sleeve gastrectomy	33
weight reduction (kg)	37.2 ( $\pm$ 17.6)
beta hydroxy butyrate ( $\mu$ Mol/l)	257.2 ( $\pm$ 444.6)
acetacetate/acetone (mg/l)	4.8 ( $\pm$ 9)

Upper level of normal for beta hydroxyl butyrate: 270  $\mu\text{mol/L}$ ; per Acetone : 50  $\text{mg/L}$



**Gli autori raccomandano di non somministrare metformina per almeno 2-3 mesi dopo chirurgia bariatrica**

# Metformin

- **is the first-line drug for diabetes**
- Metformin hydrochloride is absorbed in the upper small intestine
- Metformin has a relatively low oral bioavailability (ranges 29-60%)
- Metformin absorption is rate-limiting step in drug disposition because absorption is transporter dependent and saturable, which causes bioavailability to diminish as dosage increases

# Effect of Gastric Bypass Surgery on the Absorption and Bioavailability of Metformin

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LEE-ANN LANGKAAS, LPN<sup>3</sup>

DAN W. BIRCH, MD<sup>4</sup>  
SHAHZEER KARMALI, MD<sup>4</sup>  
DION R. BROCKS, PHD<sup>2</sup>

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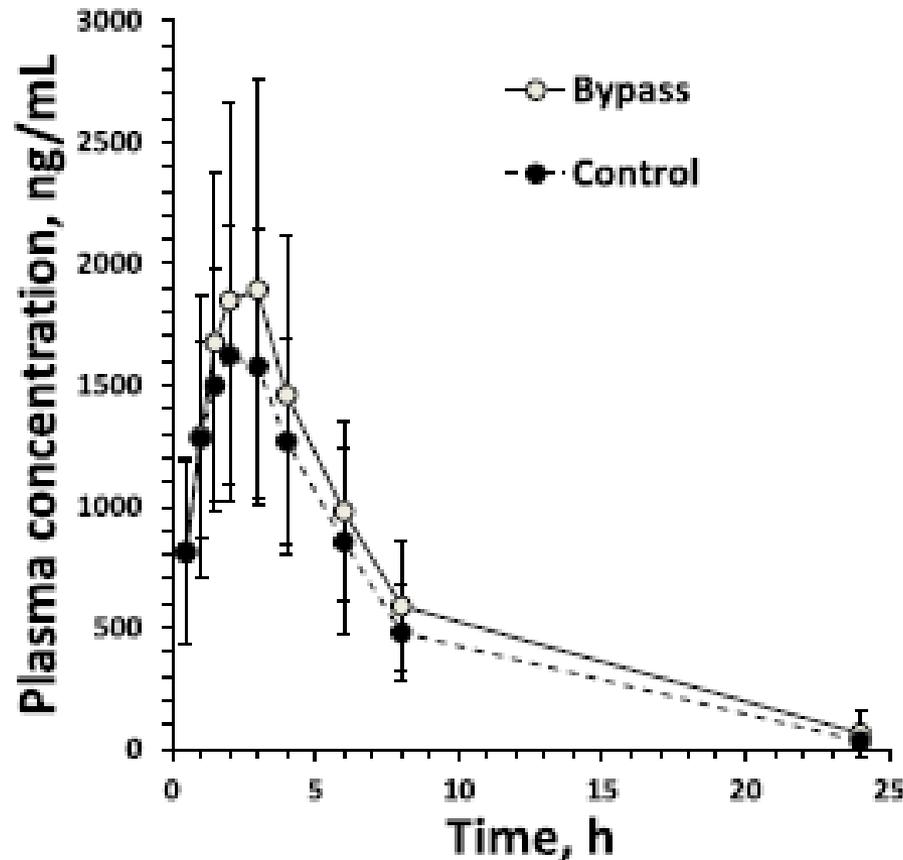
Single-dose pharmacokinetic study

Variable	Gastric bypass subjects	Control subjects	P
n	16	16	
Age (years)*	44.4 (10.0)	43.5 (11.7)	0.82
Female sex†	13 (82)	13 (82)	NA‡
BMI (kg/m <sup>2</sup> )*	38.0 (7.9)	40.5 (6.9)	0.36
Weight (kg)*	104.0 (29.0)	114.6 (26.1)	0.30
Preoperative BMI (kg/m <sup>2</sup> )*	51.5 (10.3)	—	—
Preoperative weight (kg)*	141.1 (35.9)	—	—
Time elapsed after bypass (months)*	17 (13.5)	—	—
Creatinine (μmol/L)*	62.9 (9.8)	65.2 (11.8)	0.56
Creatinine clearance (mL/min)*	91.3 (25.7)	95.7 (25.4)	0.63
A1C (%)*	5.5 (0.3)	5.6 (0.6)	0.28
Fasting glucose (mmol/L)*	4.4 (0.4)	5.1 (0.6)	0.0006
AST (units/L)*	22.6 (5.4)	25.3 (6.6)	0.22
Total cholesterol (mmol/L)*	3.96 (0.69)	4.78 (1.08)	0.02
Triglycerides (mmol/L)*	1.0 (0.33)	1.5 (0.88)	0.29§
HDL cholesterol (mmol/L)*	1.1 (0.25)	1.1 (0.38)	0.74
LDL cholesterol (mmol/L)*	2.4 (0.53)	3.0 (1.02)	0.03
Hypertension†	8 (50)	7 (43.8)	1.0
Type 2 diabetes†	1 (6.3)	0 (0)	1.0
Dyslipidemia†	1 (6.3)	4 (0.25)	0.33
Hypothyroidism†	3 (0.38)	2 (0.13)	1.0
Sleep apnea†	7 (43.8)	4 (0.25)	0.46
Gastrointestinal reflux†	1 (6.3)	4 (0.25)	0.33

# Disegno dello studio

- Al **tempo 0** ingestione di **2 cps di metformina da 500 mg (glucophage)**
- Prelievo ai tempi 0.5-1-1.5-2-3-4-6-8 ore
- Pasto standardizzato somministrato dopo 2 e 6 ore, e snack standardizzato dopo 4 ore (tot calorie 1000; 60% carboidrati)
- Raccolta urine per 24 ore dal tempo 0 per dosaggio delle concentrazioni urinarie di metformina.

# Metformin plasma concentration time curve



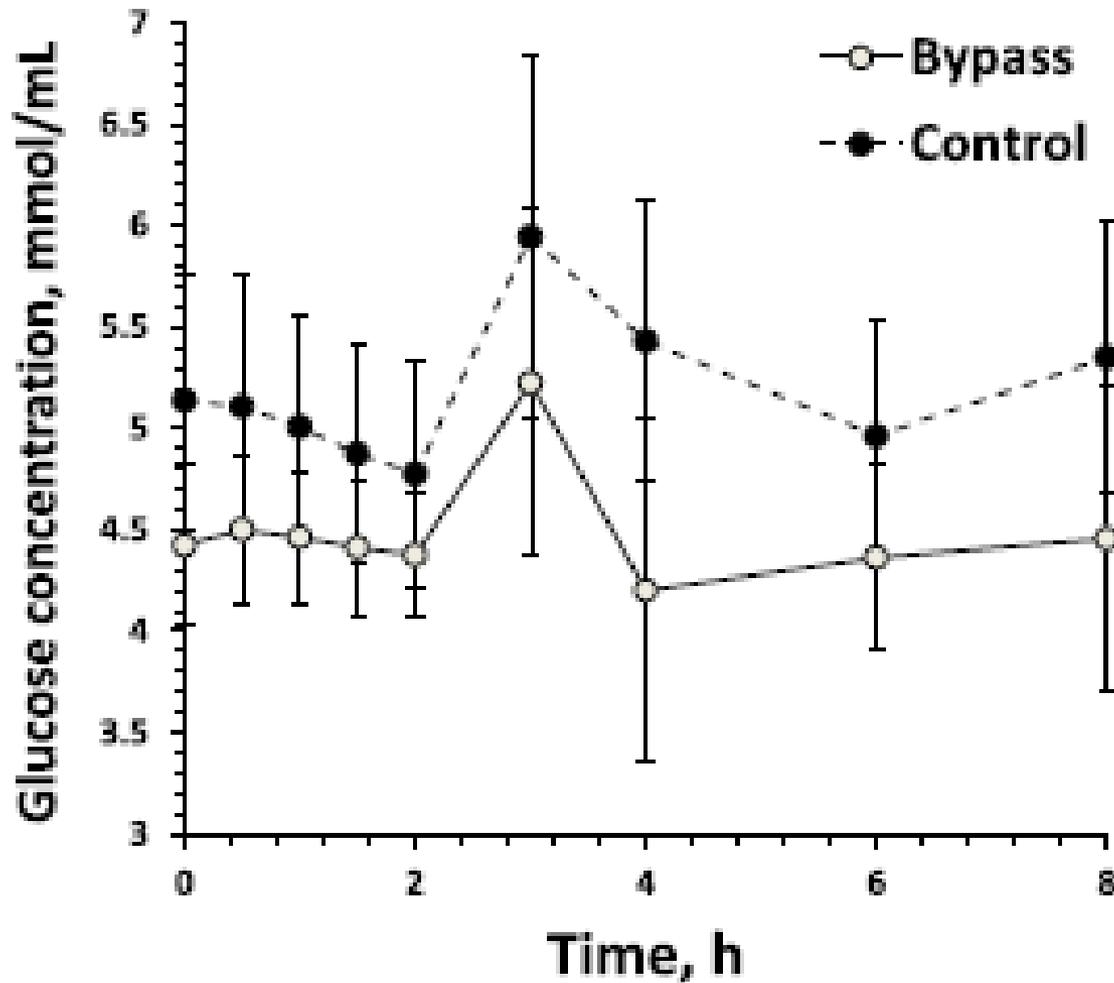
Non-significant 21% increases in the AUC concentration in RYBP patients compared with control subjects  
13.7 vs 11.4 ug/mL/h

# Gastric bypass and metformin absorption

Table 2—Pharmacokinetic and pharmacodynamic outcomes

Variable	Gastric bypass subjects	Control subjects	Mean difference (95% CI)	P
<i>n</i>	16	16		
Pharmacokinetic outcomes				
AUC <sub>0-∞</sub> (μg/h/mL)	13.7 (6.0)	11.4 (3.6)	2.3 (-1.3 to 5.9)	0.20
Bioavailability (%)	41.8 (16.2)*	27.8 (10.4)	14.0 (4.1–23.9)	0.007
AUC <sub>0-24 h</sub> (μg/h/mL)	13.4 (5.7)	11.1 (3.6)	2.2 (-1.3 to 5.6)	0.20
C <sub>max</sub> (μg/mL)	2.0 (0.86)	1.8 (0.61)	0.2 (-0.3 to 0.8)	0.32
T <sub>max</sub> (h)	3.0 (1.5–3.0)†	3.0 (1.5–3.0)†	0 (0)†	0.89†
Half-life (h)	3.9 (0.74)	4.0 (0.87)	-0.1 (-0.7 to 0.5)	0.66
Urinary recovery (0–24 h) (mg)	326 (126)	217 (81)	140 (41–239)	0.007
Weight-normalized urinary recovery (0–24 h; mg/kg)	3.1 (1.2)*	2.0 (0.78)	1.5 (0.5–2.5)	0.003
Renal clearance (mL/min)	461 (199)*	337 (131)	125 (1.5–248)	0.047
Weight-normalized renal clearance (mL/min/kg)	4.3 (1.6)*	3.0 (1.0)	1.3 (0.3–2.3)	0.009
Weight-normalized volume of distribution (L/kg)	1.4 (0.4)	1.0 (0.4)	0.4 (0.1–0.7)	0.02
Pharmacodynamic outcome				
AUC glucose <sub>0-8 h</sub> (mmol/mL/h)	35.8 (3.7)	41.7 (4.1)	5.9 (3.1–8.8)	0.0002

Data are means (SD), unless otherwise indicated. \*Sample size was 15. One sample was lost. †Numbers are median (range). Mann-Whitney *U* statistic used.



The AUC-glucose concentration in RYBP patients were 14% lower compared with control subjects ( $p < 0.05$ )

**Figure 2**—*Glucose concentration time curve.*

# Effect of Gastric Bypass Surgery on the Absorption and Bioavailability of Metformin

- L'assorbimento e la biodisponibilità della Metformina risultano più elevate dopo intervento di bypass gastrico
-  Possibili implicazioni per il dosaggio del farmaco e rischio di tossicità
- Sono necessari ulteriori studi per confermare questo dato e per delinearne il potenziale meccanismo

# conclusioni

In pazienti diabetici sottoposti a chirurgia bariatrica, e nei pazienti che dopo remissione presentano recidiva di diabete

- La metformina rappresenta il farmaco di prima scelta
- La terapia insulinica va attentamente dosata sulla base dei profili glicemici
- E' indispensabile uno stretto follow-up diabetologico per la gestione della terapia antidiabetica e delle altre comorbidità
- Sono auspicabili protocolli di terapia condivisi con algoritmi di trattamento per raggiungere l'obiettivo del compenso glicemico ottimale



Grazie per l'attenzione