Metabolic Surgery for Type 2 Diabetes
- Window into Pathophysiology-

Prof. Francesco Rubino, MD

Chair of Bariatric and Metabolic Surgery
King's College London
London, UK

September 15, 2014
DISCLOSURE SLIDE

- NGM Biopharmaceuticals (SAB Member)
- Fractyl Laboratories (Advisor/Consultant)
Surgery and Physiology

Surgical manipulations of anatomy have played a major role in advancing knowledge about physiology and disease

Surgery has helped advance understanding the functioning of:

- Central nervous system
- Pituitary gland
- Adrenals
- Pancreas
Bariatric Surgery and Metabolic Disease

“criteria ex juvantibus”

making an inference about disease causation from observations on the response of the disease to a treatment
Surgical Treatment of Type 2 Diabetes:

Clinical Outcomes
Preoperative

Female, 42yo, BMI 31
On Insulin and Multiple OHAs

2 Weeks after RYGB Blood Glucose Levels

3 Months after RYGB Blood Glucose Levels

Hyperglycemia (BG>180mg/dl)
Normal blood sugar (BG btwn 70-180)
Hypoglycemia (BG<70mg/dl)
An Instructive Case:

Female, 42yo; BMI: 31
T2DM; Dyslipidemia, Hypertension

Diabetes

No Diabetes

HBA1C

<table>
<thead>
<tr>
<th>Series1</th>
<th>0</th>
<th>1M</th>
<th>3M</th>
<th>6M</th>
<th>9M</th>
<th>12M</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.1</td>
<td>7.2</td>
<td>6.5</td>
<td>6.1</td>
<td>5.7</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Graph showing HBA1C levels over time:
- Pre-op
- 2 weeks
- 1 month
- 1 year
Association of Bariatric Surgery With Long-term Remission of Type 2 Diabetes and With Microvascular and Macrovascular Complications

Lars Sjöström, MD, PhD; Markku Peltonen, PhD; Peter Jacobson, MD, PhD; Sofie Ahlin, MD, PhD; Johanna Andersson-Assarsson, PhD; Åsa Anveden, MD; Claude Bouchard, PhD; Björn Carlsson, MD, PhD; Kristjan Karason, M.D., Ph.D; Hans Lönnroth, MD, PhD; Ingmar Näslund, MD, PhD; Elisabeth Sjöström, MD; Magdalena Taube, PhD; Hans Wedel, PhD; Per-Arne Svensson, PhD; Kajsa Sjöholm, PhD; Lena M. S. Carlsson, MD, PhD

Figure 1. Prevalence of Diabetes Remission in the Bariatric Surgery and Control Groups

<table>
<thead>
<tr>
<th>Follow-up Time, y</th>
<th>Percentage Without Diabetes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
</tr>
<tr>
<td>2</td>
<td>135</td>
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<tr>
<td>10</td>
<td>236</td>
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<tr>
<td>15</td>
<td>62</td>
</tr>
</tbody>
</table>

Total participants: Control, 207; Surgery, 303. Odds ratio (95% CI): 13.3 (8.5-20.7) for 2 years; 5.3 (2.5-9.8) for 10 years; 6.3 (2.1-18.9) for 15 years.

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

<table>
<thead>
<tr>
<th>Follow-up Time, y</th>
<th>Percentage Without Diabetes</th>
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<tbody>
<tr>
<td></td>
<td>&lt;1 y</td>
</tr>
<tr>
<td>2</td>
<td>139</td>
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<tr>
<td>10</td>
<td>82</td>
</tr>
<tr>
<td>15</td>
<td>82</td>
</tr>
</tbody>
</table>

Diabetes duration at baseline: <1 y, 1-3 y, ≥4 y.
Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials

Viktoria L Gloy junior researcher, Matthias Briel assistant professor, Deepak L Bhatt professor, Sangeeta R Kashyap associate professor of medicine, Philip R Schauer medical director, professor of surgery, Geltrude Mingrone professor, Heiner C Bucher director, Alain J Nordmann associate professor

- 11 studies, 796 patients, BMI 27-53
- Surgery superior to med Rx
  - Wt. loss, HbA1c, T2DM remission, TG, HDL, remission of metabolic syndrome, QOL, medication reduction
- No CV events or death after surgery
- Anemia (15%), Reoperation (4-8%)
BMI < 35 vs. BMI ≥ 35
Change in HbA1c

B Glycated Hemoglobin According to Body-Mass Index

<table>
<thead>
<tr>
<th>Month</th>
<th>Medical &lt;35 BMI</th>
<th>Medical ≥35 BMI</th>
<th>Surgical &lt;35 BMI</th>
<th>Surgical ≥35 BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(percentage points)</td>
<td>(percentage points)</td>
<td>(percentage points)</td>
<td>(percentage points)</td>
</tr>
<tr>
<td>0</td>
<td>9.1 (8.9)</td>
<td>8.8 (8.5)</td>
<td>9.4 (9.1)</td>
<td>9.3 (9.2)</td>
</tr>
<tr>
<td>3</td>
<td>7.2 (6.8)</td>
<td>7.1 (6.8)</td>
<td>6.7 (6.9)</td>
<td>6.4 (6.2)</td>
</tr>
<tr>
<td>6</td>
<td>7.9 (6.9)</td>
<td>7.2 (6.7)</td>
<td>6.6 (6.6)</td>
<td>6.4 (6.1)</td>
</tr>
<tr>
<td>9</td>
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<td>36</td>
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<td>303</td>
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<td>15</td>
<td>62</td>
<td>115</td>
</tr>
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Total participants
- Control: 207
- Surgery: 303

Odds ratio (95% CI)
- Total participants
  - Control: 13.3 (8.5-20.7)
  - Surgery: 5.3 (2.8-9.8)
  - Odds ratio: 6.3 (2.1-18.9)

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

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<th>15</th>
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<tbody>
<tr>
<td>&lt;1 y</td>
<td>139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 y</td>
<td></td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>≥4 y</td>
<td></td>
<td>60</td>
<td>24</td>
</tr>
</tbody>
</table>
STAMPEDE Trial: QoL Changes

• Gastric Bypass: 5/8 domains improved

• Sleeve Gastrectomy: 2/8 domains improved

• Intensive Med Rx: 0/8 domains improved

Schauer et al. NEJM 2014
Original Investigation

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Figure 3. Cumulative Incidence of Microvascular and Macrovascular Diabetes Complications in the Surgery and Control Groups

Log-rank P < .001
HR, 0.44 (95% CI, 0.34-0.56)

Log-rank P = .001
HR, 0.68 (95% CI, 0.54-0.85)

No. at risk
Control: 260 251 239 222 201 177 146 104 68 46 19
Surgery: 343 336 326 318 301 280 257 207 160 112 63

Follow-up Time, y
Cumulative Incidence, %
Control group
Surgery group

Control group
Surgery group
## Bariatric Surgery Associated With Reduced Long-Term, All-Cause Mortality Compared With Non-Operated Controls

<table>
<thead>
<tr>
<th>Study</th>
<th>Procedure</th>
<th>F/U</th>
<th>Mortality Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacDonald, 1997</td>
<td>RYGB</td>
<td>9 yr</td>
<td>88%</td>
</tr>
<tr>
<td>Flum, 2004</td>
<td>RYGB</td>
<td>4.4 yr</td>
<td>33%</td>
</tr>
<tr>
<td>Christou, 2004</td>
<td>RYGB</td>
<td>5 yr</td>
<td>89%</td>
</tr>
<tr>
<td>Sowemimo, 2007</td>
<td>RYGB</td>
<td>4.4 yr</td>
<td>63%</td>
</tr>
<tr>
<td>Dixon, 2007</td>
<td>LAGB</td>
<td>12 yr</td>
<td>72%</td>
</tr>
<tr>
<td>Adams, 2007</td>
<td>RYGB</td>
<td>8.4 yr</td>
<td>40%</td>
</tr>
<tr>
<td>Sjostrom, 2007</td>
<td>VBG/other</td>
<td>14 yr</td>
<td>31%</td>
</tr>
<tr>
<td>Perry, 2008</td>
<td>RYGB/LAGB</td>
<td>2 yr</td>
<td>48%</td>
</tr>
</tbody>
</table>
Is there something special in the mechanism of action of bariatric surgery?
BI Gastrectomy       BII-Gastrectomy     RY-Gastrectomy RYGB
DIABETES AND OPERATION.

A NOTE ON THE EFFECT OF GASTRO-JEJUNOSTOMY UPON A CASE OF MILD DIABETES MELLITUS WITH A LOW RENAL THRESHOLD.

By O. LEYTON, M.D. Camb., F.R.C.P. Lond.,
Physician to the London Hospital.

How can we account for the apparent improvement? The glycosuria was absent after operation in spite of a diet containing a fair amount of carbohydrate. In order to determine whether the operation

THE AMELIORATION OF DIABETES MELLITUS FOLLOWING SUBTOTAL GASTRECTOMY

MURRY N. FRIEDMAN, M.D., F.A.C.S., ANTONIO J. SANCETTA, M.D., and GEORGE J. MAGOVERN, M.D., Brooklyn, New York

In 1923, MURLIN noted the presence of a substance in extracts of the pancreas which could raise the blood sugar. Subsequently, this hyperglycemic factor was demonstrated and duodenum. Therefore, when subtotal gastrectomy for duodenal ulcer resulted in marked amelioration of the diabetic state in 3 patients at the Brooklyn Veterans Hosp
Reports of Diabetes Remission after Bariatric Surgery Procedures

- Jejuno-ileal bypass
  - Ahmad et al; Diabetes Care 1978
- Verical banded gastroplasty
  - Neve HJ et al; Obesity Surg 1993
- Biliopancreatic diversion
  - Scopinaro et al; WJS 1998
- Gastric Bypass
  - Printen et al; Am Surg 1979
  - Pories et al; Ann Surg. 1987
  - Pories et al; Ann Surg 1992
Despite surgical control of diabetes was reported since 1925, the effect (and opportunity) remained unknown to the scientific community through the XX century.

- Segmentation of medical specialties in XX-century medicine
- Diabetes considered invariably chronic and progressive disease > things that cannot be explained are often looked with skepticism in medicine
- Prevailing view that obesity leads to diabetes and that weight loss improves hyperglycemia > surgical control of diabetes after bariatric surgery not enough “incongruous” to inspire new hypothesis
- For most of the XX-century the GI tract was regarded as merely a tube for digestion and absorption of nutrients
- As an implicitly organ-focused intervention, surgery could not be seen as a rational solution for a systemic disease such as diabetes.
First Protocol for a Randomized Clinical Study of Diabetes Surgery Submitted to IRB (Mount Sinai Medical Center, New York)

RCT comparing Gastric Bypass Surgery vs Intensive Medical Therapy in patients with BMI 30–35

The IRB does not approve
Effect of Duodenal–Jejunal Exclusion in a Non-obese Animal Model of Type 2 Diabetes
A New Perspective for an Old Disease

Francesco Rubino, MD, and Jacques Marescaux, MD, FRCS

**Background:** The Roux-en-Y gastric bypass and the biliopancreatic diversion effectively induce weight loss and long-term control of type 2 diabetes in morbidly obese individuals. It is unknown whether the control of diabetes is a secondary outcome from the treatment of weight loss, or is related to specific anatomical or physiological changes that reduce insulin resistance and improve beta-cell function. These findings suggest a potential role of the proximal gut in the pathogenesis of the disease and put forward the possibility of alternative therapeutic approaches for the management of type 2 diabetes.

*(Ann Surg 2004;239: 1–11)*

![Graph showing OGTT results for different groups: Diet, Bypass, Sham.](image)

**GK-Rat**
Lean, type 2 diabetes
Hyperinsulinism
Insulin resistance
*(Nature Genetics 1996)*
Effect of Duodenal–Jejunal Exclusion in a Non-obese Animal Model of Type 2 Diabetes

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First experimental evidence that diabetes resolution is a weight-independent, direct effect of GI surgery

**Rationale for DIABETES SURGERY**
Gastrointestinal Bypass Improves Glucose Homeostasis in Rodents by Weight Independent Mechanisms

GK-Rat (Lean)
Rubino et al, Ann Surg 2004
Kindel et al J Gastr Surg 2009
Saberi et al (Diabetes 2013)

Obese mice
Troy et al, Cell Metabolism, Sept 2008

Streptoz. Diabetes

Type 1 Diabetes

Obese - Diabetic rat
Rubino et al, Endocrinology 2005
Saberi et al, Diabetes 2013
Patel et al. Obesity 2013
Mechanisms of Action of GI Surgery
2004-2014
How Does Surgery work?
Mechanisms of Surgical Control of Diabetes

- Gut Hormones
- Bile Acids
  - intestinal glucose re-programming (Science 2013)
  - intestinal gluconeogenesis
  - others

- Microbiota
- Nutrient Sensing
Glucose-lowering effect of DJB in absence of insulin

Non-obese type 1 diabetic mice

Breen et al.  
*Nature*  Medicine 2012
<table>
<thead>
<tr>
<th><strong>Courtesy of Dr Lee Kaplan</strong></th>
<th>Gastric Band</th>
<th>Sleeve Gastrex</th>
<th>RYGB</th>
<th>DJB</th>
<th>BPD</th>
<th>Ileal Interposition</th>
<th>Endoluminal Sleeve</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric Restriction</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>±</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrectomy</strong></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
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</tr>
<tr>
<td><strong>Altered gastric function</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td><strong>Gastric exclusion</strong></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
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<tr>
<td><strong>Duodenal exclusion</strong></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td><strong>Enhanced distal nutrient delivery</strong></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td><strong>Malabsorption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
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<tr>
<td><strong>Partial vagotomy</strong></td>
<td>±</td>
<td></td>
<td>✓</td>
<td></td>
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</tbody>
</table>
Evidence for anti-diabetic effects of proximal intestinal bypass
All improve Diabetes, although with different potency and likely distinct mechanisms.

**RCTs and clinical series suggest**

**Gradient BPD > RYGB > Sleeve > Banding**
Lower Intestinal vs. Upper Intestinal Hypothesis?

Duodenal (Jejunal) Exclusion

Gastro-jejunal Anastomosis
(enhanced distal delivery of nutrients)

G-J Anastomosis alone does not Improve Diabetes in Rats

OGTT GK rats

Glucose levels (mg/dl) vs. Time (min)

- GK DJB
- GK Sham
- GK GJ

Rubino et al; Annals of Surgery Nov 2006
Adding Doudenal Exclusion to GJ improves diabetes in rats

Rubino et al; Annals of Surgery Nov 2006
Restoration of Duodenal Passage after DJB worsens glucose tolerance

Rubino et al; Annals of Surgery Nov 2006
Duodenal (Jejunal) Exclusion

Improves DM in rats

Gastro-jejunal Anastomosis

No Effect on DM in rats
Duodenal Jejunal Exclusion has distinct anti-diabetic effects

ELS Improves IP Glucose Tolerance (Kaplan et al)
rapid rise and fall of postprandial GLP-1

Effects of SG not abolished in GLP-1R KO mice (Wilson-Perez et al; Diabetes 2013)

Injection of GLP1-R Antagonist does not reverse improvement of diabetes in humans who had RYGB (Jimenez et al; Diabetes Care 2013)

GLP-1 not the principal mediator of Diabetes remission after bariatric surgery
Bypass of the Proximal Intestine:

How Does it Work?

Other endocrine mechanisms?

Paracrine mechanisms?

Changes in gut microbiota?

Alterations in bile acid metabolism?

Changes in nutrient sensing mechanisms?

Anti-incretins?

Others?
Is Type 2 Diabetes an Operable Intestinal Disease?

A provocative yet reasonable hypothesis

Francesco Rubino, MD

TYPE 2 DIABETES: IS IT AN INTESTINAL DISEASE? — The rapid resolution of diabetes after Roux-
The incretin effect

- 70% of post-glucose insulin secretion is due to the incretin effect
- The incretin effect is due to gut hormones;
Glucose Lowering Mechanisms in the Postprandial State

Nutrients Passage in the GI Tract Induces:

- Suppression of ghrelin
- Increase in GLP-1/GIP
- Suppression of Glucagon
- Increase in Insulin

- Reduction of hepatic glucose production (nutrient sensing) (Lam et al, Nature)
- Increased intestinal glucose uptake (Stilopulous et al Science 2013)

>>> GLUCOSE LOWERING EFFECT
Anti-incretin Theory

Foodborne stimuli may cause exaggerated/untimely activation of anti-incretin mechanisms, which may act as a diabetogenic factor.
Anti-incretin Theory may Explain Benefits and Complications of RYGB

- Improvement / Remission of T2DM

- Postprandial Hyperinsulinemic Hypoglycemia
  Uncontroled β-cell proliferation
Glucose Excursions after Alterations of GI Anatomy Suggest Disruption of Physiologic Incretin/Anti-Incretin Balance
Predictions

Excess anti-incretin results in IR and/or beta-cell Dysfunction/depletion

>> gut factors from subjects with IR or diabetes should be able to induce IR in normal cells/subjects
Jejunal Proteins Secreted by db/db Mice or Insulin-Resistant Humans Impair the Insulin Signaling and Determine Insulin Resistance

S. Salinari, C. Debard, A. Bertuzzi, C. Durand, P. Zimmet, H. Vidal, G. Mingrone

PLOS ONE 2013

Proteins from duodenum-jejunum of diabetic mice (db/db)

Normal Mice Soleus Muscle

L-cells skeletal muscle

Intraperitoneal Insulin Tolerance Test (IPITT)

Normal, Swiss Mice

Insulin Resistance

Reduced Insulin Sensitivity (minimal model)
Predictions

incretin/anti-incretin balance ensures control of beta-cell proliferation/growth

- Uncoupling or net reduction of anti-incretin mechanisms by disruption of GI anatomy can cause beta-cell proliferation
Beta-Cell Proliferation after RYGB/DJB Suggests Disruption of Physiologic Regulation of Beta-Cell Growth

RYGB vs Sham Operation in non diabetic animals (pigs)

RYGB > Increased in β-cell mass,
   Increased islet number
   increased number of extraislet β-cells
   Lindqvist et al; Diabetes May 2014 63:5 1665-1671

Decreased beta-cell loss in GK rats after DJB
(Speck M et al; Am J Phys End Met 2011)

Nesidioblastosis after RYGB in humans
(Service et al; NEJM 2005)

Heterotopic (gastric) pancreatic mass after RYGB in humans
(Guimares et al; BMC Surg 2013)
Is the Gut the “Sweet Spot” for the Treatment of Diabetes?

Diabetes 2014;63:1–4  DOI: 10.2337/db14-0402

Oskar Minkowski possessed a rare combination of talents: He was an internist with the intuition of a scientist and the dexterity of a surgeon. One day in 1889, he and his assistant, Walther Bauhin, performed the first pancreaticoduodenectomy (PD) in a human. They observed that the patient, a 23-year-old man with severe diabetes, survived and was no longer hyperglycemic. This procedure was repeated on several other patients with similar results. Minkowski and Bauhin hypothesized that the nutrient indigestion that was occurring in the patients’ intestines was responsible for their hyperglycemia. They proposed that a portion of the stomach be removed in addition to the duodenum, which would interrupt nutrient intake and thereby lower blood glucose levels. This procedure, known as the Whipple procedure, is now considered a standard treatment for certain types of pancreatic cancer. Minkowski and Bauhin’s work laid the foundation for modern surgical treatment of diabetes and continues to be relevant today.

Diabetes, July 2014, in press
3rd World Congress on Interventional Therapies for Diabetes &
2nd Diabetes Surgery Summit (DSS)

LONDON, UK
SEPTEMBER 2015

the most important event

in *Diabetes and Metabolic Surgery*

More to come…
Acknowledgements

International Collaborations

David Cummings, Seattle (USA)
Lee Kaplan, (Boston, USA)
Phil Schauer, (Cleveland USA)
Geltrude Mingrone, (Rome, Italy)
Marco Castagneto, (Rome, Italy)
Carel le Roux, (Dublin, Ireland)
Tim McGraw (New York, USA)
Ricardo Cohen, (Brasil)
Joel Leroy, (Strasbourg, France)
Jaques Marescaux (Strasbourg, France)
Stephanie Amiel (London, UK)
George Alberti (London, UK)
Paul Zimmet (Melbourne, Australia)
John Dixon (Melbourne, Australia)
Michel Gagner (Montreal, Canada)

Strasbourg’s Lab (2000-2007)
Antonello Forgione
Stefano Sereno

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Jaques Marescaux (Strasbourg, France)
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George Alberti (London, UK)
Paul Zimmet (Melbourne, Australia)
John Dixon (Melbourne, Australia)
Michel Gagner (Montreal, Canada)

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Alpana Shukla
M. Moreira
S. M Ahn
Nogma Whyne

KCL Metabolic Surgery Lab
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Patricia Fonseca
Angelo Sereno
Ileana Geogloman

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