Remission of Diabetes after Bariatric Surgery
New Insights into Mechanism of Action

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March 20, 2015
Orlando, FL
Prevalence (%) of Diabetes in (20-79 years), 2011

Data source: WHO
Countries/Territories of Number of People with Diabetes (20-79 years), 2011 & 2030

<table>
<thead>
<tr>
<th>COUNTRY /TERRITORY</th>
<th>2011 MILLIONS</th>
<th>COUNTRY /TERRITORY</th>
<th>2030 MILLIONS</th>
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<tbody>
<tr>
<td>1 China</td>
<td>90.0</td>
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<td>129.7</td>
</tr>
<tr>
<td>2 India</td>
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<td>101.2</td>
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<td>4 Russian Federation</td>
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<tr>
<td>10 Indonesia</td>
<td>7.3</td>
<td>10 Pakistan</td>
<td>11.4</td>
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</tbody>
</table>

Data source: WHO report
Escalating Diabetes Epidemic in China

Pan et al. Diabetes Care 1994; Gu et al. Diabetologia 2003; Yang et al. NEJM 2010

Hu F B Dia Care 2011;34:1249-1257
Prevalence of Obesity (age 20yr +)
Year 2008

Data source: WHO
Obesity Trends* Among U.S. Adults
BRFSS, 1990, 2000, 2010
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

Source: Behavioral Risk Factor Surveillance System, CDC.
Epidemics of T2DM in Relation to Obesity

Natural History of T2DM

Obesity → Pre-Diabetes → Diabetes ---→ Uncontrolled Hyperglycemia

IGT/IFG

-25 -15 -5 0 5 15 25 35 Years

Plasma Glucose
120 mg/dL

Relative beta-cell Function (%)

100%

Insulin Resistance

Fasting

Post-Prandial

Insulin Secretion

Adapted from International Diabetes Center (Minneapolis, MN)
March 6, 2015
Paradigm of T2DM Control

Exercise

Diet

Weight Loss

Preservation of
Insulin Sensitivity

Preservation of
Beta Cell Function

Minimize Hypoglycemia

Prevent Complications

Minimize Hyperglycemia

Minimize Hypoglycemia
Current Oral Therapies for T2DM

Kidney Excretion/Reabsorption

SGLT2 Inhibitor

Hyperglycemia

Pancreas

Impaired insulin secretion

↑ Sulfonylureas
↑ Repaglinide
↑ Nateglinide

Glucose

Gut

↓ α-Glucosidase inhibitors
Sitagliptin
Pramlintide
Exenatide

Muscle

↓ Glucose uptake

Liver

↑ Hepatic glucose output

↓ Biguanide
↓ TZDs

Adipose

↑ TZDs, ↑ Biguanide
Rosiglitazone, Metformin, Glyburide

Kahn SE, et al. NEJM 2006; 355(23): 2427-2443

March 6, 2015
Current Incretin Treatment for T2DM

Drucker DJ. Diabetes Care 2003; 36:2929-2940
Current Surgical Treatment for T2DM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

- Intensive medical therapy
- Roux-en-Y gastric bypass
- Sleeve gastrectomy

**A Change in Glycated Hemoglobin**

<table>
<thead>
<tr>
<th>Value at Visit</th>
<th>Baseline</th>
<th>3</th>
<th>6</th>
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<th>12</th>
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<td>Roux-en-Y gastric bypass</td>
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<td>6.6</td>
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</table>

**B Change in Fasting Plasma Glucose**

<table>
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<tr>
<th>Value at Visit</th>
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</table>
Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

C  Average No. of Diabetes Medications

<table>
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<tr>
<th>Value at Visit</th>
<th>Baseline</th>
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<td>0.3</td>
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<td>1.1</td>
<td>0.9</td>
<td>0.8</td>
<td>0.9</td>
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</table>

D  Change in BMI

<table>
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<th>Value at Visit</th>
<th>Baseline</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
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<td>31.3</td>
<td>28.3</td>
<td>27.3</td>
<td>27.2</td>
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</tbody>
</table>
Mechanisms of Action of the Bariatric Procedures: Mandatory Life Style Modification

- Caloric restriction
  - Beta cell function improved in just two days
  - Peripheral insulin resistance improved over a period
  - Hepatic insulin sensitivity remains unchanged

- Satiety alteration

- Changes in eating behavior
  - Tends to consume more low fat diet

- Patient support group and patient education
Mechanisms of Action of the Bariatric Procedures: Energy Imbalance

• Malabsorption
• Energy expenditure (Controversial)
  – Some reported decrease secondary to weight loss after RYGB
  – Others reported increase in both RYGB and BPD
Mechanisms of Action of the Bariatric Procedures: Gastrointestinal Microflora

• Established during the first year of life, influenced by a variety of environmental and metabolic factors, relatively stable during adulthood

• Links between gut flora and metabolism have been discovered

• Two major bacterial species: Bacteroidetes & Firmicutes
  – Obese subject: higher level of Firmicutes, lower level of Bacteroidetes
  – Related to efficiency of energy harvest
  – Firmicutes decreases after bariatric surgery *

DISCOVERY OF GASTROINTESTINAL HORMONES

Rehfeld J, 2004
Mechanisms of Action of the Bariatric Procedures: Metabolic Effects (Entero-Hormones)

- **Glucagon-Like Peptide-1 (GLP-1):**
  - Secreted by L cell in distal ileum and colon
  - Increases after the metabolic procedures with intestinal bypass (RYGB, BPD, BPD-DS)
  - Increases along with accelerated gastric transit time (LSG)

- **Glucose-Dependent Insulinotropic Polypeptide (GIP):**
  - Secreted by K cell in duodenum and proximal jejunum
  - Changes after bariatric surgery remain controversial
  - More report decrease after RYGB and BPD
  - No change after LAGB
  - Change undetermined after LSG
Mechanisms of Action of the Bariatric Procedures: Metabolic Effects (Entero-Hormones)

• Peptide YY (PYY)
  – Secreted by L cell in distal ileum and colon, and brain
  – Inhibit gastric emptying and intestinal motility (ileal break); decrease appetite through direct central mechanism
  – Level increase after RYGB, BPD and LSG, not LAGB

• Growth Hormone-releasing Peptide (Ghrelin)
  – Mainly secreted by the oxyntic glands in the fundus of the stomach, also in intestine
  – Negatively affect glucose homeostasis
  – Become lower after LSG
  – Level controversial after RYGB

March 6, 2015
Mechanisms of Action of the Bariatric Procedures: 
Metabolic Effects (Entero-Hormones)

• Cholecystokinin (CCK)
  – Secreted in duodenum and proximal jejunum
  – A potent inducer of satiety
  – Level change controversial after bariatric surgery

• Oxyntomodulin
  – Founded in colon, produced by oxyntic cells of the fundic mucosa
  – Increased after RYGB, not LAGB
Mechanisms of Action of the Bariatric Procedures: Metabolic Effects

• Bile acids increase
  – Increase energy expenditure in brown adipose tissue
  – Binding to nuclear receptor FXR, improve glucose tolerance

• Adipose tissue inflammatory markers
  – Proinflammatory cytokines decreases: TNF, IL-6, Leptin
  – Anti-inflammatory hormone increases: adiponectin
Foregut hypothesis

• The exclusion of the duodenal nutrient passage may offset an abnormality of gastrointestinal physiology responsible for insulin resistance and type 2 Diabetes

• Enhanced secretion of something good for glucose homeostasis?

• Reduced production of something bad for glucose homeostasis?
A: Duodenal-jejunal bypass  
B: Gastrojejunostomy  
C: Sham-operated

- Male 10wk GK rats
- Control: age matched Wistar rats
OGTT – 10 days after Surgery

OGTT GK rats

Annals of Surgery Nov 2006
Exclusion of Various Segment of Small Intestine

A) Duodenum
B) Jejunum
C) Ileum

G-K Rats, Male, 8-10 wks, n=8 each group
Exclusion of Duodenum and Proximal Jejunum Should be Enough for Blood Glucose Normalization
Pilot Clinical Study of an Endoscopic, Removable Duodenal-Jejunal Bypass Liner for the Treatment of Type 2 Diabetes

Leonardo Rodriguez, M.D., M.B.S.,¹ Eliana Reyes, M.D.,¹ Pilar Fagaldia, M.D.,¹ Maria Soledad Otia, M.D.,¹ Jorge Saba, M.D.,¹ Carmen Gloria Aylwina, M.D.,¹ Carolina Prieto, M.D.,¹ Almino Ramose, M.D., M.B.S.,² Manoel Galveoa, M.D., M.B.S.,² Keith S. Gersina, M.D.,³ and Christopher Soril, M.D.⁴

Abstract

Background: Bariatric surgery is associated with the rapid improvement of type 2 diabetes (T2DM). Here we report an exploratory trial of a completely endoscopic, removable, duodenal jejunal bypass liner (DJBL) intended to treat T2DM.

Methods: Obese T2DM subjects were randomized to receive a DJBL (n = 12) or sham endoscopy (n = 6) in a 24-week study, extended up to 52 weeks. Measurements included weights, hemoglobin A1c (HbA1c), meal tolerance testing, fasting glucose, and seven-point glucose profiles. Subjects' diets were adjusted in the first 2 weeks to obtain similar weight loss during this period.

Results: Subjects had baseline HbA1c of 9.1 ± 1.7% and body mass index of 38.9 ± 6.1 kg/m² (±SD). In the complete population by week 1, change in fasting glucose in the DJBL arm was −55 ± 21 mg/dL versus +42 ± 30 mg/dL in the sham arm (P = 0.05; ±SE); the seven-point glucose profiles were reduced in the DJBL arm but not in the sham arm. Mean postprandial glucose area under the curve was reduced in the DJBL arm by 20% and increased by 30% in the sham arm (P = 0.016). At week 12, HbA1c change was −1.3 ± 0.9% in the DJBL arm and −2.1 ± 0.4% in the sham arm (P < 0.05) and at 24 weeks, values were −2.4 ± 0.7% in the DJBL arm and −0.8 ± 0.4% in the sham arm (P = 0.05). Device migrations required endoscopic removal prior to reaching 52 weeks.

Conclusions: The DJBL rapidly normalized glycemic control in obese T2DM subjects, a promising development in the search for novel therapies less invasive than bariatric surgery.
Figure 2. Ex vivo appearance of the duodenal–jejunal bypass sleeve fully deployed. Drawstrings (solid arrow) are present at the self-expanding anchor (dotted arrow) to allow for device removal. The 60-cm impermeable sleeve provides proximal jejunal exclusion.

Figure 1. Diagram of duodenal–jejunal bypass sleeve anchored within the duodenal bulb (arrow) and fully deployed.
Metabolic Effect Induced by Intestinal Exclusion

**Graph E**

% Change in Postprandial Glucose AUC (mg/dL·min)

- **DJBL**
- **Sham**

<table>
<thead>
<tr>
<th>Week</th>
<th>DJBL</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Significant difference

**Graph F**

Median Body Weight Change (kg)

- **DJBL**
- **Sham**

**Median Weight Change from Baseline (kg)**

<table>
<thead>
<tr>
<th>Treatment (week)</th>
<th>DJBL</th>
<th>Sham</th>
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<tbody>
<tr>
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<td>16</td>
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<td>20</td>
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<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Metabolic Effect Induced by Intestinal Exclusion

A. Week 12 and Week 24

- DJBL
  - Week 12: n=8
  - Week 24: n=9

- Sham
  - Week 12: n=3
  - Week 24: n=4

B. Fasting Plasma Glucose Change from Baseline (mg/dL)

- DJBL
- Sham

C. DJBL 7 point glucose profile

- Blood Glucose (mg/dL)
  - Baseline
  - Week 1

D. Sham 7 point glucose profile

- Blood Glucose (mg/dL)
  - Baseline
  - Week 1

3/6/2015
Hindgut hypothesis

- Nutrients reach the distal ileum within 5 min of the ingestion of food and this stimulates the secretion of GLP-1 by L cells located in this area.

Mason E. Obes Surg 2005 15, 459461
GLP-1 Antagonist Can Eliminate the Metabolic Effect after DJB

**Figure 8** An OGTT was performed in male, GK rats 6 weeks after DJE (n=8) or DJE Sham (n=6) surgery. Plasma glucose concentrations were measured at 0, 15, 30, 60, 90, and 120 min after a 2 g/kg D-glucose oral gavage with the co-administration of 200 μl of saline (a) or 200 μl of 25 nM of the GLP1R antagonist Ex-9 (b) subcutaneously. (c) depicts glucose concentration AUC for the 6-week OGTT. *Statistically different for the designated time points (a and b) or between groups (c) when p<0.05. Data are presented as mean±SE.
Fibroblast growth factors 19 and 21

FGF19 serum levels increase following RYGB surgery

- Higher levels of circulating FGF21 were associated with diabetes and various cardiometabolic disease phenotypes

Tuesday, February 10, 2015  -  14:01
Owen Masklin  -  Editor in chief, Bariatric News

Fibroblast growth factors 19 and 21 (FGF19 and FGF21) circulating levels and hepatic gene expression of the associated signalling pathway are significantly dysregulated in type 2 diabetes, according to research published in PlosOne. FGF19 serum levels are significantly lower in Class III obese
FGF-19 is a Member of an Atypical FGF Subfamily

Background

- FGF19, FGF21 and FGF23 belong to an atypical FGF subfamily
- Novel signaling pathway
  - Act as endocrine ligands
  - Show dramatically reduced binding to HSPG
  - FGFR-mediated signaling requires klotho co-receptors
FGF-19 is predominantly expressed in the ileum.

Expression of FGF-19 in ileum is further induced by bile acid.
FGF-19 is a Novel Endocrine Hormone

- FGF-19 is a novel metabolic regulator
  - Functions as an enterohepatic signal to regulate bile acid homeostasis
  - Ectopic expression of FGF-19
    - Increases metabolic rate
    - Confers resistance to diet-induced obesity
    - Improves glucose tolerance in animal disease models

- Bile acid metabolism
- Glucose homeostasis
- Lipid metabolism
- Gallbladder emptying

- Liver
- Adipose

- FGFR4
- FGFR1c
- B-Klotho

- FGF-19
- FGF-21
Plasma FGF-19 Increased after RYGB, But not after Non-surgical Weight Loss

• Graph unpublished. Will show graph when giving speech
Circulating FGF19 Decreases, while FGF21 Increases in T2DM Patients

<table>
<thead>
<tr>
<th>Diabetes Status</th>
<th>N</th>
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<td>FGF21 No-T2D</td>
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<td>792.91</td>
<td>524.44</td>
<td>233.31</td>
<td>817.93</td>
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</table>

Diabetic patients had significantly lower FGF19 serum levels (pg/mL), and higher (trending) FGF21 serum levels (pg/mL). P-values according to the Wilcoxon Rank sum test (\(^*\): P-value, 0.0036; \(^\circ\): P-value, 0.0871).

doi:10.1371/journal.pone.0116928.t001
FGF-19 Level is Reduced in Patients with Metabolic Syndrome and Diabetes

Table II. Differences in measured parameters according to metabolic syndrome presence.

<table>
<thead>
<tr>
<th>Type</th>
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<td>&lt;0.01</td>
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<td></td>
<td></td>
<td>478.4</td>
<td>848.7</td>
<td>242.4</td>
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</tbody>
</table>

![Box plot showing FGF-19 serum values](image)

Metabolic Syndrome (n=66) vs Healthy Volunteer (n=136)

![Box plot showing FGF-19 serum values](image)

T2D (n=42) vs Healthy Volunteer (n=136)

Stejskal et al. SJCLR (2008), 68 (6), 501-507
FGF-19 Injection can Decrease both Body Weight and Plasma Glucose Level

- Graph unpublished. Will show graph when giving speech
FGF-19 Increases $\beta$-Cell Mass in $db/db$ Mouse Pancreas

- Graph unpublished. Will show when giving speech
Unpublished Data: DJB Prevents Pancreatic Beta Cell Degradation and Promotes Regeneration

• The ideal treatment of T2DM:
  – Restoration of insulin sensitivity
    • Peripheral
    • Hepatic
  – Restoration of pancreatic beta cell mass and function
    • Beta cell regeneration
    • Prevention from apoptosis and necrosis
The ideal treatment of T2DM:

- Restoration of insulin sensitivity
  - Peripheral
  - Hepatic
  - Been confirmed by numerous data

- Restoration of pancreatic beta cell mass and function
  - Beta cell regeneration
  - Prevention from apoptosis and necrosis
  - No solid data support
Study Design

• Normal healthy Wistar rats, Male
• All undergo DJB procedure to cause post-operative metabolic effect, sham as control
• i.p. STZ to induce beta cell necrosis
• Test beta cell function
• Histology of pancrease
Fasting Plasma Glucose Level

• DJB + STZ group has a significantly lower FPG than Sham + STZ group
• Will show graph when giving speech
i.p. Glucose Tolerance Test

• DJB + STZ group has a significantly lower glucose excursion than Sham + STZ group
• DJB + STZ group has a better insulin response upon glucose challenge than DJB + Sham
• Unpublished. Will show when giving speech
DJB + STZ group has a significantly higher plasma GLP-1 level (both fasting and post-glucose challenge) than Sham + STZ group.

Unpublished. Will show when giving speech.
• DJB + STZ group has a better beta cell mass than Sham + STZ group
• Unpublished. Will show when giving speech
Summary

• Bariatric surgery is an effective treatment for selected T2DM patients

• Its underlying mechanism is unclear yet, however, may includes the following:
  – Life style modification caused by the surgery
    • Caloric restriction
    • Satiety alteration
    • Change in eating behavior
    • Patient support group and patient education
  – Energy imbalance
    • Malabsorption
    • Energy expenditure
  – Gastrointestinal Microflora
    • Bacteroidetes & Firmicutes
Summary

– Metabolic effect (GI Hormons)
  • GLP-1
  • GIP-1
  • CCK
  • PYY
  • Ghrelin
  • Oxyntomodulin
  • etc.

– Cytokins
  • IL-6
  • TNF
  • Leptin
  • Adiponectin
  • etc.
Summary

– Bile Acid
  • FGF-19

– Pancreatic beta cell protection and regeneration
  • Bariatric surgery is beneficial to beta cells
  • To be further confirmed
Thanks!
Questions

1. Which gastrointestinal microflora bacterial species has an increased level in obese subject?
   A. Bacteroidetes
   B. Firmicutes
   C. Spirochaetes
   D. Fibrobacteres
   E. Planctomycetes
   F. lactobacilli and streptococci.

2. In T2DM patients, which description is correct?
   A. Plasma FGF-19 level decreases, while FGF-21 level increases
   B. Plasma FGF-19 level increases, while FGF-21 level decreases
   C. Both plasma FGF-19 and FGF-21 levels increase
   D. Both plasma FGF-19 and FGF-21 levels decrease
   E. None of them changes

Answer: 1. B; 2. A

March 6, 2015