Role of Bariatric Surgery in less obese diabetic patients
-Perspectives of endocrinology-

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1. Bariatric Surgery in **morbidly obese patients** with Type 2 Diabetes

2. Bariatric Surgery in **non-morbidly obese patients** with Type 2 Diabetes
Restrictive
- Adjustable Gastric banding

Mixed
- Roux-en-Y Gastric Bypass

Malabsorptive
- Biliopancreatic diversion
Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

Philip R. Schauer, M.D., Sangeeta R. Kashyap, M.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., John P. Kirwan, Ph.D., Claire E. Pothier, M.P.H., Susan Thomas, R.N., Beth Abood, R.N., Steven E. Nissen, M.D., and Deepak L. Bhatt, M.D., M.P.H.

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 Castagnero, M.D., Giovanni Ghirlanda, M.D., and Francesco Rubino, M.D.
Preop. BMI 36 kg/m²

<table>
<thead>
<tr>
<th></th>
<th>Intensive medical therapy</th>
<th>Roux-en-Y gastric bypass</th>
<th>Sleeve gastrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intensive medical therapy</strong></td>
<td>![Graph]</td>
<td>![Graph]</td>
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<tr>
<td><strong>Sleeve gastrectomy</strong></td>
<td>![Graph]</td>
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<tr>
<td><strong>RYGB</strong></td>
<td>![Graph]</td>
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</tbody>
</table>

The proportion of patients with a glycated hemoglobin level of 6% or less 12 months after randomization.

- **Intensive medical therapy** → 12%
- **Sleeve gastrectomy** → 37%
- **RYGB** → 42%

Glycated Hemoglobin Levels during 2 Years of Follow-up.

Preop. BMI 45 kg/m²

Remission

Medical therapy 0%

Gastric bypass 75%

Biliopancreatic diversion 95%

• Preoperative BMI and weight loss did not predict the improvement in hyperglycemia after bariatric surgery
• Mingrone points out, “suggesting that BMI should not be used as the sole criterion for selection of patients with T2DM for bariatric surgery”.

Criteria other than BMI, such as insulin pancreatic reserve and the degree of insulin resistance, should also be taken into account when selecting patients for bariatric surgery.

Identifying *preoperative predictors of diabetes remission* is critical for determining which diabetic patients will obtain *the greatest benefit from surgery*!
Predictors of Diabetes Resolution

• The Shortest duration (<5yrs)
• The Mildest form of T2DM (diet controlled)
• Greatest weight loss after surgery
  most likely to achieve complete resolution of T2DM  *Ann Surg* 2003;238:467-485
• Preoperative treatment with oral antidiabetic agents
• Smaller preoperative waist circumference (peripheral fat distribution)
• Shorter duration of diabetes
  predicted diabetes resolution  *J Gastrointest Surg* 2005;9:1112-6
• Preserved β-cell function; Less deterioration in β-cell function at the time of surgery may maximize the effect of the surgery-altered secretion of gut peptides that enhance β-cell insulin secretion  *Ann Intern Med.* 2009;150:94-103
<table>
<thead>
<tr>
<th></th>
<th>Remission of diabetes</th>
<th>Nonremission of diabetes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.2 ± 10.3</td>
<td>44.6 ± 10.9</td>
<td>0.655</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/24</td>
<td>6/10</td>
<td>0.567</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.5 ± 2.6</td>
<td>34.5 ± 2.7</td>
<td>0.989</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>105.1 ± 7.2</td>
<td>101.4 ± 5.3</td>
<td>0.220</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>4.3 ± 3.4</td>
<td>7.4 ± 3.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>OHA (oral hypoglycemic agents)</td>
<td>24 (70.6%)</td>
<td>6 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>10 (29.4%)</td>
<td>10 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Fasting C-peptide (ng/ml)</td>
<td>3.81 ± 1.98</td>
<td>3.33 ± 1.21</td>
<td>0.383</td>
</tr>
<tr>
<td>Stimulated C-peptide (ng/ml)</td>
<td>9.85 ± 5.78</td>
<td>7.23 ± 4.38</td>
<td>0.085</td>
</tr>
<tr>
<td>ΔC-peptide (ng/ml)</td>
<td>6.18 ± 5.16</td>
<td>3.90 ± 3.88</td>
<td>0.093</td>
</tr>
<tr>
<td>A₁C (%)</td>
<td>8.28 ± 1.35</td>
<td>9.40 ± 1.62</td>
<td>0.013</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>190.2 ± 43.3</td>
<td>205.5 ± 69.6</td>
<td>0.427</td>
</tr>
<tr>
<td>Visceral fat area (cm²)</td>
<td>165.3 ± 47.9</td>
<td>213.3 ± 59.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Subcutaneous fat area (cm²)</td>
<td>352.0 ± 116.7</td>
<td>290.2 ± 87.2</td>
<td>0.066</td>
</tr>
<tr>
<td>Visceral-to-subcutaneous fat area ratio</td>
<td>0.53 ± 0.26</td>
<td>0.79 ± 0.29</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Preop. BMI 34.5 kg/m²**

**RYGB**

**12 months A₁C (%)**

5.7 vs. 7.2, P<0.001

*Kim MK, Song KH et al. Obesity (Silver Spring). 2011;19(9):1835-9*
Visceral obesity is a negative predictor of remission of diabetes one year after bariatric surgery.

*Kim MK, Song KH et al. Obesity (Silver Spring). 2011;19(9):1835-9*
Insulin Sensitive Vs. Insulin Resistant
Possible factors associated with diabetes non-remission or re-emergence

- Older age
- Male gender
- Lower preoperative BMI
- Diabetes duration > 10 years
- Insulin use
- Inadequate weight loss and weight regain
- Surgery type: LAGB vs. sleeve gastrectomy vs. RYGB vs. BPD
- Severity of preoperative $\beta$-cell dysfunction (i.e. hyperglycaemia)
- Inadequate incretin stimulation following surgery?
• Gut hormones play a role in diabetes remission after a RYGB.
• Our aim was to investigate differences in gut hormone secretion according to diabetes remission after surgery.
Before surgery

AUC of active GLP-1; 95.3 vs 527 pg/ml·hr−1, P=0.04

Before surgery

12 months after surgery


12 months after surgery

Before surgery

C-peptide (ng/mL)

Insulin (mU/L)

Time (min)
# Gut peptide change after RYGB

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>RYGB</th>
<th>BPD</th>
<th>LAGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghrelin</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>GIP</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>GLP-1</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Peptide YY</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

**Peak active GLP-1;**
643 vs 537 pg/ml, *P=NS*
• Remission of diabetes after RYGB is not associated with a difference in gut hormone secretion.

• Patients remaining diabetic had higher insulin resistance and decreased β-cell functional reserve.

• Reduced insulinotropic potencies of the incretin hormones are the most important mechanism behind the reduced incretin effect.

Summary-1

• Visceral obesity is a negative predictor of remission of diabetes one year after RYGB.

• Failure of diabetes remission after RYGB is not caused by a defective increase in GLP-1 secretion, but instead largely by impaired β-cell responses to GLP-1.

• This is consistent with the conclusions of a previous study that surgical treatment might be more successful in patients with a less aggressive form of type 2 diabetes.

• Earlier intervention increases the likelihood of remission.

• Bariatric surgery for the severely obese with type 2 diabetes should be considered early as an option for eligible patients, rather than being held back as a last resort.
Possible factors associated with diabetes non-remission or re-emergence

- Older age
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- Lower preoperative BMI
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- Surgery type: LAGB vs. sleeve gastrectomy vs. RYGB vs. BPD
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- Inadequate incretin stimulation following surgery?

*Clinical considerations for the management of residual diabetes following bariatric surgery*  
*Diabetes, Obesity and Metabolism 2012 Epub ahead*
Re-emergence of diabetes after gastric bypass in patients with mid-to long-term follow-up

Percent EWL (%) vs Follow Up Time

- Remission
- Recurred

Surg Obes Relat Dis. 2010;6:249-253
Lessions from “outcome after gastrectomy in gastric cancer patients with type 2 diabetes”

• 국내

• 403 gastric cancer patients with T2DM

• Preop. BMI 24.7 kg/m²

→ FU(33 mon.) BMI 21.2 kg/m²

• T2DM was cured in 15% and was improved in 30%

• The BMI reduction ratio was the most influential factor on T2DM status

Lessons from “outcome after gastrectomy in gastric cancer patients with type 2 diabetes”
DuodenoJejunal Bypass

Duodenal-jejunal bypass (DJB) surgery achieved glycemic control in non-obese rats with DM *in the absence of weight loss or decreased caloric intake.*
Body weight -4.3kg ↓

Preop. BMI 25.3 kg/m² (range 23-29)

HbA1c; 8.1 vs. 7.4%, P=NS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of Type 2 Diabetes (years)</th>
<th>Preoperative Medication</th>
<th>Medication at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NPH 26 units</td>
<td>Metformin 1700mg</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Glimepride 4mg</td>
<td>Gliclazide 80mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metformin 1000mg</td>
<td>Metformin 1000mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acarbose 200mg</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Glargine 36 units</td>
<td>Glimepride 4mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voglibose 0.9 mg</td>
<td>Metformin 1700mg</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>Glimepride 3mg</td>
<td>Gliclazide 80mg</td>
</tr>
<tr>
<td></td>
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<td>Metformin 1000mg</td>
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<td>Voglibose 0.9 mg</td>
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<td>6</td>
<td>3</td>
<td>Glimepride 3mg</td>
<td>Metformin 1000mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metformin 1700mg</td>
<td>Pioglitazone 15mg</td>
</tr>
</tbody>
</table>
• DJB increased GLP-1 secretion over six months in non-morbidly obese type 2 diabetic patients

DJB-Case (38/M)
DJB-Case (38/M)

- Insulin
- HbA1c (%)
- Body weight (kg)

2009 2010 2011 2012
OP
OP
• Improvements in glycemic control after DJB may be *less impressive in subjects with a lower BMI*. 

Diabet Med 2011; 28: 628-642
Mechanism of Remission of Diabetes after RYGB

Early mechanism
- Caloric restriction
  - Gut peptide changes
  - Weight loss

Late mechanism
- Caloric restriction
  - Gut peptide changes
  - Weight loss
• Bariatric surgery improves both insulin secretion (via early hormonal mechanisms) and insulin sensitivity (via early caloric restriction and later weight loss).

• **Caloric restriction and weight loss are the dominant mechanisms** responsible for improved glucose metabolism after bariatric surgery.

• Changes in the pattern of gastrointestinal hormone release may support the early adaptation of β-cell function but are unlikely to make a major contribution to insulin action.

*Diabetes Care 2009;32:514-520.*
BMI cutoff points in Asian

- A World Health Organization (WHO) expert panel recommended potential BMI categories for public health action in people of Asian (i.e., underweight $< 18.5\text{kg/m}^2$, increasing but acceptable risk 18.5 to $< 23\ \text{kg/m}^2$, increased risk 23 to $< 27.5\ \text{kg/m}^2$, and high risk $\geq 27.5\ \text{kg/m}^2$).

The BMI cutoff value was 24 kg/m² in South Asian, and **25 kg/m² in Chinese** for the equivalent incidence rate of diabetes at a **BMI of 30 kg/m² in white subjects**.
Bariatric surgery: an IDF statement for obese Type 2 diabetes

<table>
<thead>
<tr>
<th>BMI range</th>
<th>Eligible for surgery</th>
<th>Prioritized for surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 kg/m²</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>30–35 kg/m²</td>
<td>Yes—conditional †‡</td>
<td>No</td>
</tr>
<tr>
<td>35–40 kg/m²</td>
<td>Yes</td>
<td>Yes—conditional †‡</td>
</tr>
<tr>
<td>&gt; 40 kg/m²</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*In all cases, patients should have failed to lose weight and sustain significant weight loss through non-surgical weight-management programmes, and have Type 2 diabetes that has not responded adequately to lifestyle measures (± metformin) with a HbA₁c < 53 mmol/mol (7%).

†Action points should be lowered by 2.5 BMI point levels for Asian people [74].

‡HbA₁c > 58 mmol/mol (7.5%) despite fully optimized conventional therapy, especially if weight is increasing, or other weight responsive co-morbidities not achieving targets on conventional therapies. For example, blood pressure, dyslipidaemia and obstructive sleep apnoea.

Diabet Med 2011; 28: 628-642
Asian Consensus Meeting on Metabolic Surgery

• Bariatric surgery should be considered as a treatment option for obesity in people with Asian ethnicity above a **BMI of 30 kg/m²** if they have **central obesity** (waist circumference more than 80 cm in females and more than 90 cm in males) along with at least **two of the additional criteria for metabolic syndrome**: raised triglycerides, reduced HDL cholesterol levels, high blood pressure and raised fasting plasma glucose levels

OBES SURG 2010; 20: 929-936
IFS0-APC Consensus Statements 2011

• Bariatric surgery should be considered for the treatment of obesity for acceptable Asian candidates with $\text{BMI} \geq 35$ with or without co-morbidities

• should be considered for the treatment of T2DM or metabolic syndrome for patients who are inadequately controlled by lifestyle alternations and medical treatment for acceptable Asian candidates with $\text{BMI} \geq 30$

• may be considered as a non- primary alternative to treat inadequately controlled T2DM, or metabolic syndrome, for suitable Asian candidates with $\text{BMI} \geq 27.5$.

OBES SURG 2012; 22: 677-684
Inclusion criteria

• 제2형 당뇨병

• 나이: 18-60세

• 현재 BMI ≥ 30 kg/m²

• 공복 C-peptide ≥ 1.0ng/ml 이면서 식후 2시간 C-peptide ≥ 1.5ng/ml

• 수술에 대한 이해를 하고 있으며 동기가 확실하며 수술 후 칼슘, 비타민 등의 섭취 및 추적관찰에 순응할 환자

August 19, 2009
Exclusion criteria

**Absolute**
- 제1형 당뇨병, 유전적, 약품, 화학제로 인한 당뇨병인 경우
- 과거 복부 질환 수술로 복강경수술이 불가능한 경우
- **Coagulopathy**, 간경변
- 임신 중
- 정신저체나 심신 허약자로 수술 결정에 대한 판단이 어려운 경우
- 알코올이나 약물 남용
- 중대한 정신질환
- 중대한 심혈관질환 (뇌출혈, 뇌경색증, 부정맥, 협심증)
- **Serum Creatinine > 2mg/dL**
  or **DM CKD Stage IV, V (eGFR < 30ml/min)**

**Relative**
- 체장염의 과거력
- 당뇨병의 이환기간 > 10년
- 인슐린치료 > 7년

August 19, 2009
Integration into diabetes treatment algorithms

Diet & Exercise

Metformin

Pioglitazone

GLP-1 agonist

Insulin

Bariatric Surgery

Obese Type 2 DM
Risks

• Perioperative complications
• Gastrointestinal complications
• Macro- and micro-nutrients deficiency
• Osteoporosis
• Wernicke’s encephalopathy (rarely)
• Hypoglycemia

Benefits

• Weight loss
• Improved glycemia
• CV risk reduction
• All-cause mortality ↓
• Improvements in health-related quality of life
• Osteoarthritis, obstructive sleep apnea
Summary-2

• There were only limited data about the benefits of bariatric surgery on the glycemic control of non-morbidly obese patients with T2DM (BMI < 30 kg/m² in people with Asian ethnicity)

• Caloric restriction and **weight loss** are the dominant mechanisms responsible for improved glucose metabolism after RYGB.

• Bariatric surgery should be considered for the treatment of T2DM in people with Asian ethnicity above a **BMI of 30 kg/m²**
Is surgery the universal panacea for obese patients with type 2 diabetes?

**Not yet**