Bariatric to metabolic surgery

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Prevalence of Diabetes in Korea

Prevalence: 10% + IGT: 20% = 30%

PREVALENCE OF DIABETES 2010
(≥ 30 YRS OLD)

3.2 Million

IMPAIRED FASTING GLUCOSE (PREDIABETES)

6.2 Million

DIABETES FACT SHEET
IN KOREA 2012

Korean Diabetes association (KDA)/Korea Centers for Disease Control and Prevention (CDC)
Diabetes fact sheet in Korea 2012
Korean Diabetes Association (KDA)/Korea Centers for Disease Control and Prevention (CDC)

Diabetes Fact Sheet in Korea 2012

Korean has ethnical singularity of T2DM

<table>
<thead>
<tr>
<th></th>
<th>Korea</th>
<th>China</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>9.1%</td>
<td>9.3%</td>
<td>10.9%</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>4.2%</td>
<td>4%</td>
<td>35%</td>
</tr>
</tbody>
</table>

BMI less than 25 kg/m² (50%)

Mean BMI of Korean Diabetes; 25.2 kg/m²

BMI < 23

BMI > 30

BMI more than 25 kg/m²

BMI > 23 < 24.9

Korean Diabetes Association (KDA)/Korea Centers for Disease Control and Prevention (CDC)

Diabetes fact sheet in Korea 2012
Compared to Caucasians, East Asian patients with type 2 diabetes have a lower body mass index (BMI) and impaired beta cell function. (than insulin resistance)

Metabolic surgery for T2DM with low body mass index and impaired pancreatic function
Conclusions
Gastric bypass is now established as an effective and safe therapy for morbid obesity and its associated morbidities. No other therapy has produced such durable and complete control of diabetes mellitus.

Why the operation controls diabetes so well is not clear, but the major reason appears to be the reduction of caloric intake. There is some evidence that changes in the incretin stimulation of the islets by the gut may also play a role.
Foregut has a role for development of T2DM
But didn’t know exactly.

Anyway They opened the possibility of surgical treatment for non obese T2DM.

Chronic exaggerated stimulation of proximal gut
Induce overproduction of factor that cause
Impairment of incretin action and induce hyperglycemia.

The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes.
The incretin is very important to glucose metabolism

Incretin effect is increased secretion of insulin when glucose is taken orally than to infused intravenously.

An estimated 50–70% of insulin secretion after glucose ingestion is attributable to this observation, which is now known as the ‘incretin effect’.
GIP and GLP-1 are the only incretin hormone in humans. Furthermore, studies have shown that these 2 peptides potentiate glucose stimulated insulin secretion in an additive manner, likely contribute equally to the incretin effect, and together can fully account for the incretin effect in humans.

*Biography of incretins: GLP-1 and GIP.*
Nutrient in the bowel lumen stimulate enteroendocrine cells. (secretion is made by in response to nutrient, not food residue) They have strong inotropic effect to insulin secretion. But this action was deactivated by DPP4.

GIP secretion requires nutrient absorption, (SGLT1, GPR 40.....) whilst the mere presence of nutrients in the lumen is sufficient to trigger GLP-1 secretion.
In type 2 DM

GIP concentration is increased, and insulinotropic actions are significantly attenuated.

Concentration of GLP-1 decreased but insulinotropic action is preserved.
Causes of rapid increased diabetic population T2DM in Asia

Increasing overall and abdominal obesity
Decreased function and cell mass of beta-cell in pancreas
Developmental origins of diabetes: Epigenetics
Nutrition transition and changes in diet and life style

Not due to amount of food
But due to eating habit

Higher glycemic index, and Glycemic load value.
Polished rice, refined wheat

*Diabetes in Asia: epidemiology, risk factors, and pathophysiology.*
Glucose-dependent insulinotropic polypeptide (GIP) is a hormone mainly produced in the proximal segments of the bowel. It has been shown that GIP is overproduced in patients with obesity and T2DM, whereas the production of GLP-1 deficiency was also demonstrated in patients with type 2 diabetes.

An abundant high-glycemic-index diet provokes fast, early, and intense absorption; as an obvious consequence, proximal segments of the small bowel are forced to overwork, whereas distal parts are exposed to proportionally fewer nutrients.

Glucose-dependent insulinotropic polypeptide (GIP) is a hormone mainly produced in the proximal segments of bowel. It has been shown that GIP is overproduced in patients with obesity and T2DM, whereas the production of GLP-1 deficiency was also demonstrated in patients with type 2 diabetes.

The pathophysiologic function of GLP-1 and GIP
GLP-1 actions in peripheral tissues

Released in response to Nutrient in Distal gut

Depletion of nutrient to stimulate hindgut, so insufficient release of GLP-1 From L-cell is problem.

insulinotropic action of GLP-1 is Preserved in any situation.

Biology of incretins: GLP-1 and GIP.
Baggio LL, Drucker DJ.
Emerging novel medical treatment is incretin based medication.

Dipeptidyl peptidase-4 inhibitors
- Sitagliptin: FDA approval 2006 (Januvia)
- Vildagliptin: FDA approval 2007 (Galvus)
- Saxagliptin: FDA approval 2009 (Onglyza)
- Linagliptin: FDA approval 2011 (Trajenta)

GLP-1 receptor agonist
- Exendin-3
- Exendin-4 (saliva of the lizard Gila monster)
- Exenatide, Byetta (synthetic version of Exendin-4) approved FDA 2005
- Liraglutide (Victoza): long acting GLP-1 agonist approved FDA 2010 (97% homology)
- LAPS-Exendin (long acting GLP-1 agonist, 1/month)
Incretin based treatment is more effective to Korean diabetic subjects.


Effects of a 6-Month Exenatide Therapy on HbA1c and Weight in Korean Patients with Type 2 Diabetes: A Retrospective Cohort Study

Juyoung Shin, Jin-Sun Chang, Hun-Sung Kim, Sun-Hee Ko, Bong-Yun Cha, Ho-Young Son, Kun-Ho Yoon, Jae-Hyoung Cho
Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Juyoung Shin, Jin-Sun Chang, Hun-Sung Kim, Sun-Hee Ko, Bong-Yun Cha, Ho-Young Son, Kun-Ho Yoon, Jae-Hyoung Cho
Effects of a 6-Month Exenatide Therapy on HbA1c and Weight in Korean Patients with Type 2 Diabetes: A Retrospective Cohort Study
Diabetes Metab J 2012;36:364-370
Healthy subject, the GIP is insulinotropic hormone but in hyperglycemia, insulinotropic action is attenuated. Big problem of GIP is functional diversity.

_Biology of incretins: GLP-1 and GIP_
Baggio LL, Drucker DJ.
GIP is unpredictable

Interfering the suppression of Postprandial glucagon release

GIP Receptor Down regulation
Attenuation of post prandial glucagon suppression in T2DM

Inappropriate suppression of glucagon during OGTT but not during isoglycaemic i.v. glucose infusion contributes to the reduced incretin effect in type 2 diabetes mellitus

F. K. Knop · T. Vilsbøll · S. Madsbad · J. J. Holst · T. Krarup

In diabetic subject

Postprandial glucagon suppression is attenuated with oral glucose
But IV glucose infusion: normal glucagon suppression

Attenuated and delayed glucagon suppression in patients with type 2 diabetes occurs after oral ingestion of glucose, while isoglycaemic i.v. administration of glucose results in normal suppression of glucagon. We suggest that this phenomenon contributes both to the glucose intolerance and to the reduced incretin effect observed in patients with type 2 diabetes.

glucagon suppression was attenuated by certain hormone from intestine, in response to nutrient.

Inappropriate suppression of glucagon during OGTT but not during isoglycaemic i.v. glucose infusion contributes to the reduced incretin effect in type 2 diabetes mellitus.
Knop FK, Vilsbøll T, Madsbad S, Holst JJ, Krarup T.
In type 2 diabetes, the postprandial glucagon suppression is attenuated. To find out cause of hyperglucagonemic response to orally ingested glucose.

Our results indicate that the intestinal hormones, GIP, GLP-1, and GLP-2, may play a role in the inappropriate glucagon response to orally ingested glucose in T2DM with, 

Especially, GIP, acting to increase glucagon secretion.

GIP Does Not Potentiate the Antidiabetic Effects of GLP-1 in Hyperglycemic Patients With Type 2 Diabetes

Nikolaos Mentis, Irfan Vardarli, Lars D. Köthe, Jens J. Holst, Carolyn F. Deacon, Michael Theodorakis, Juris J. Meier, and Michael A. Nauck

OBJECTIVE—The incretin glucagon-like peptide 1 (GLP-1) exerts insulinotropic activity in type 2 diabetic patients, whereas glucose-dependent insulinotropic polypeptide (GIP) no longer does. We studied whether GIP can alter the insulinotropic or glucagonostatic activity of GLP-1 in type 2 diabetic patients.

CONCLUSIONS—GIP is unable to further amplify the insulinotropic and glucose-lowering effects of GLP-1 in type 2 diabetes. Rather, the suppression of glucagon by GLP-1 is antagonized by GIP.

Diabetes 60:1270–1276, 2011

Exogenous Glucose–Dependent Insulinotropic Polypeptide Worsens Postprandial Hyperglycemia in Type 2 Diabetes

Chee W. Chia, Olga D. Carlson, Wook Kim, Yu-Kyong Shin, Cornelia P. Charles, Hee Seung Kim, Denise L. Melvin, and Josephine M. Egan

GIP infusion further worsened hyperglycemia postprandially, most likely through its suppressive effect on GLP-1. These findings make it unlikely that GIP or GIP receptor agonists will be useful in treating the hyperglycemia of patients with type 2 diabetes.

Diabetes 58:1342–1349, 2009
Exposure of islet cells to high glucose results in GIP desensitization and reduced expression of GIPR, which can be reversed by reducing hyperglycemia (Hinke et al., 2000; Piteau et al., 2007; Xu et al., 2007).


However, high glucose inhibits (PPAR) transcription via a response element (GRE) within the PPAR promoter. This causes a reduction in PPAR transcription and leads to a decrease in the PPAR expression level. With a cellular reduction in PPAR, it is no longer able to fully stimulate GIPR expression and its expression also falls. This reduction in GIPR expression causes a decreased insulin secretion in response to GIP from the cell.

recent research suggests that GIP-R antagonists may afford an entirely new class of drugs for alleviation of obesity related insulin resistance with beta-cell sparing effects. Given the close parallels between Roux-en-Y surgery in humans and studies of GIP-R blockade in animal models of obesity-diabetes, GIP-R antagonists may offer an exiting new treatment option for obesity-diabetes.

Research agenda

- Clinical studies to address the therapeutic potential of GIP-R agonists for type 2 diabetes.
- Development of alternative routes of administration/non-peptidic GIP-based therapeutics.
- Ascertainment of the role of GIP signalling in models of obesity-diabetes and surgical GIP ablation.
- GIP-R antagonism as a new drug target for obesity-diabetes.

Question is GIP-R has broad spectrum effect so they cause unexpected side effect

Strategies to reduce some actions of GIP might have potential for treating obesity, and elucidating the mechanisms by which gastric bypass procedures ameliorate diabetes might yield additional novel strategies to treat diabetes.
Summary of limitations of medical treatment (Incretin based treatment)

Side effect of GLP-1 analogue
1. Nausea
2. Pancreatitis; increased amylase release
3. Pancreatic cancer, thyroid cancer

Routes of administration for GLP-1R agonist delivery is ineffective

GIP antagonist is not available yet.

GIP-R has broad spectrum effect so they cause unexpected side effect
However, varying proportions of patients report nausea and vomiting, adverse events that typically narrow the therapeutic dose range. Furthermore, GLP-1 RAs reduce fasting glucose to a clinically meaningful extent, but not into the normal range. In contrast, where GLP-1 is administered as a short-term intravenous infusion, a full normalization of glucose concentrations (approximately 5 mmol/l) has been observed without any risk of gastrointestinal side effects.

Reasons for this may include modifications of the peptide molecules in the subcutaneous environment or high local concentrations triggering side effects through GLP-1 receptors on autonomic nerves in subcutaneous adipose tissue.

Do current incretin mimetics exploit the full therapeutic potential inherent in GLP-1 receptor stimulation?

Weight-Loss Surgery Works Better than Drugs to Control Diabetes

In the first head-to-head studies comparing weight-loss surgery to medication for diabetes, surgery proved more effective in putting the disease in remission.

By ALICE PARK | @aliceparkny | March 26, 2012 | 1
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.

Cleveland group

Medical Tx. Vs Sleeve Gastrectomy vs RnY GBP

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

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

Italian group

Medical Tx. vs RnY GBP vs BPD
Effect of glycemic control

Sleeve gastrectomy

RnY Gastric bypass

BPD (Bilio-pancreatic diversion)

Purely restrictive

Restrictive > mal-absorptive

Purely mal-absorptive

Directly proportional to the degree of weight loss and small incretin effect: GLP1↑

Dose not affect insulin resistance
But increases insulin secretion via Stimulation of nutrient mediated Incretin secretion

Amelioration of insulin sensitivity and consequently, a significant reduction of insulin secretion.

Mingrone G.
Biliopancreatic diversion > gastric bypass > Sleeve gastrectomy > Medical Tx

Figure 2. Glycated Hemoglobin Levels during 2 Years of Follow-up.
### Table 2  Mechanisms of action of bariatric surgery in improving/reverting type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Diabetes resolution (%)</th>
<th>Insulin sensitivity restoration (euglycemic hyperinsulinemic clamp)</th>
<th>Insulin secretion after OGTT or a meal</th>
<th>GIP secretion after OGTT or a meal</th>
<th>GLP-1 secretion after OGTT or a meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliopancreatic diversion</td>
<td>98.9</td>
<td>Normal</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Purely mal-absorptive</td>
<td></td>
<td>Supranormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RnY procedure</td>
<td>83.7</td>
<td>Unchanged</td>
<td>Increased</td>
<td>Increased</td>
<td>[43, 39]</td>
</tr>
<tr>
<td>Restrictive &gt; mal-absorptive</td>
<td></td>
<td>Slightly improved</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

However, very different from other animals, we started cooking, boiling, and liquefying food to make nutrients more available. Simply transforming apples into an apple puree causes significant changes in the patterns of absorption and glycemic response after a meal.

Glucose-dependent insulinotropic polypeptide (GIP) is a hormone mainly produced in the proximal segments of bowel. It has been shown that GIP is overproduced in patients with obesity and T2DM, whereas the production of GLP-1 deficiency was also demonstrated in patients with type 2 diabetes.


Pathogenesis of T2DM (incretin)
1. Beta-cell failure and decreased insulin secretion

- Macronutrients (High GI)
  - GIP over production
    - Glucagon suppression failure
    - Hyperglycemia
  - Defective release of GLP-1
    - Decreased beta-cell stimulation

- GIP receptor down regulation
  (high glucose inhibits PPAR α transcription)
Pathogenesis of T2DM (inflammation)
2. Peripheral resistance to insulin

Macronutrients

Glucolipotoxicity

Obesity (Leptin resistance)

Reactive oxygen species (ROS)

Cytokine (TNF-alpha, IL-6 CRP)

NF kappa B

Interfere Insulin signaling

Following insulin resistance will be corrected with euglycemia because the patient does not have lipotoxicity.
Tx goal of T2DM for the patient with low BMI and decreased beta cell function is revitalization to pancreas rather than weight control.

Surgical mechanism of diabetic control:

- **Caloric Restriction**

- **Changes in adipoinsular axis**

- **Changes in enteroinsular axis**

Regulatory factors:

- GIP↓
- GLP-1↑

Changes in the enteroinsular axis:

- Insulin secretion↑
- Glucagon secretion↓
- Somatostatin secretion↑
- β-cell proliferation↑
- β-cell apoptosis↓
- Insulin biosynthesis↑
Personal experience of metabolic surgery
The choice of bariatric procedure is complex requiring a careful risk-benefit analysis and acceptance of variation in regional practice and expertise.

- Expertise and experience in the bariatric surgical procedures
- The patient’s preference when the range of risks and benefits, the importance of compliance, and the effects on eating choices and behaviours have been fully described.
- The patient’s general health and risk factors associated with high peri-operative morbidity and mortality.
- The simplicity and reversibility of a procedure.
- The duration of type 2 diabetes and the degree of apparent residual beta-cell function
- The follow-up regimen for the procedure and the commitment of the patient to adhere to it.

A position statement from the international diabetes federation, 2011
Surgery is most potent, effective modality to control type 2 DM, but paradoxically, disadvantage of surgical treatment is surgery itself!!!!!!!

1. Every operation has morbidity and mortality (simplicity=safety)

2. There are lots of treatment modality of T2DM. And new medications are continuously being developed. (reversibility)

3. Entire life span, the patient may need another surgery. (simplicity)
Our hypothesis is

Loss or impaired and imbalanced incretin effect is major problem in Korean Diabetic Pt.

Single anastomosis gastric bypass with long afferent loop would be effective to normalize entero-insular axis.
Long vertical gastric tube is made along the lesser curvature from 2cm proximal to the pylorus aiming the fundus.

And small Intestine, 200cm distal to Treitz ligament, is bypassed through single anasotmosis.

The structure provides early ileal(hind gut) exposure of nutrient make L-cell stimulation

Complete exclusion of foregut From nutrient to release GIP

Simple, easy

Safety, easy reversibility
Our experience

The anastomosis is located very low in the abdomen (physiologic) An anchoring suture make parallel line Between gastric tube and small bowel
Our experience

Patient characteristics

Patients in clinical trial

• After approval of IRB for human research of Soonchunhyang University hospital
• 2009. August ~ 2013.October (It has been 4 years since first surgery)
• Soonchunhyang University Hospital
• 176 Laparoscopic single anastomosis-gastric bypass for T2DM
• All patients were recruited for treatment of DM

Inclusion Criteria

• Body Mass Index (BMI) < 30 kg/m2
• Type 2 Diabetes (definition by ADA)
• Fasting C-peptide more than 1 ng/ml
Incretin change monitoring before & after surgery

Aim

• To evaluate of effects of surgery on incretin responses to
  • oral glucose tolerance test (OGTT)

Patients and Methods

• N = 12 (F=5, M=7) Total number of patient  175
  • BMI 23 ~ 30 kg/m² (mean 26 kg/m²)
  • active GLP-1, GIP, insulin and c-peptide levels were measured by 75g OGTT before and 1 month after surgery

Inclusion criteria

• Type 2 DM (definition by ADA) and not well-controlled after 6 months medical treatment (HbA1C >7%)
• Aged 18 – 67, and had an acceptable operative risk
Incretin levels 1 month after laparoscopic single anastomosis gastric bypass surgery in non-morbid obese type 2 diabetes patients

Myung-Jin Kim, Hyeong-Kyu Park, Dong-Won Byun, Kyo-II Suh, Kyung-Yul Hur

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Figure 1 Illustration of single anastomosis gastric bypass surgery. The surgeon made a vertical gastric tube and anastomosed it with jejunum 200 cm distal from the ligament of Treitz.

GIP
GLP-1
Our experience

Glucose, Insulin, c-peptide

AUC of Insulin and c-peptide increased. AUC of glucose was decreased.
Our experience

Active GLP-1 of OGTT

Peak level & AUC was increased markedly

Expediting delivery of nutrient to distal small bowel stimulates L-cell
Peak level & AUC of GIP was significantly decreased

Exclusion of proximal small bowel from ingested nutrient to block the K-cell stimulation
Restrictive > mal-absorptive

<table>
<thead>
<tr>
<th></th>
<th>Restrictive</th>
<th>&lt; mal-absorptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIP after OGTT</td>
<td>Increased</td>
<td>Reduced</td>
</tr>
<tr>
<td>GLP-1 after OGTT</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Purely mal-absorptive

**Figure from Mingrone G. Insulin sensitivity and secretion modifications after bariatric surgery. J Endocrinol Invest. 2012 Jul;35(7):692-8.**

Mingrone G.

Mini Gastric bypass

BPD (Bilio-pancreatic diversion)
Glucagon and GIP secretions are enhanced in RYGB subjects after meal

Why GIP increases in RnY GBP?

GIP in RnY GBP

Location of defunctionalized limb

Early exposure of nutrient
To Roux-limb- K cell stimulation

Bariatric surgery
(absorption of nutrient)

Metabolic surgery
(in response to nutrient)

Depends on the length of biliopancreatic limb
The length is different surgeon to surgeon.
Our experience

Changes in mean HbA1c

Stagnation between 1st~2nd year
Changes of mean BMI

- Preop: 25.2
- 1st year: 22.8
- 2nd year: 22.5
- 3rd year: 22.4
Our experience

HbA1c vs BMI (independent?)

Preop 1st 2nd 3rd Year

Preop 1st 2nd 3rd Year
Our experience

High preop. HbA1c group

Preop 1st 2nd 3rd Year

Preoperative HbA1C > 9

Low preop. HbA1c group

Preop 1st 2nd 3rd Year

Preoperative HbA1C < 9
Our experience

Preoperative BMI 25>

Preoperative BMI 25<
### Our experience

Late complication (mostly early period of experience)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastomosis stenosis</td>
<td>1 (convert to RNY)</td>
</tr>
<tr>
<td>Marginal ulcer</td>
<td>19</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>12</td>
</tr>
<tr>
<td>Marginal ulcer perforation</td>
<td>1</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica</td>
<td>1</td>
</tr>
<tr>
<td>(Zinc deficiency)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative hospital stay (day)</td>
<td>4.7 (3-7)</td>
</tr>
</tbody>
</table>

- Diathetic, allergic to all suture material
- Non absorbable Stitch marginal ulcer
- Enterocutaneous fistula
Our experience

Changes in mean HbA1c

- Preop: 9.19%
- Year 1: 6.9%
- Year 2: 6.7%
- Year 3: 5.9%

Early and delayed response
Effects of Exenatide on Measures of β-Cell Function After 3 Years in Metformin-Treated Patients With Type 2 Diabetes

Prolonged exposure to elevated glucose and lipid concentrations is detrimental to beta-cell function. These combined glucolipotoxic effects result in impaired insulin secretion and beta-cell apoptosis, and may contribute to the loss of beta-cell function in the pathogenesis of type 2 diabetes.

Exposure to GLP-1 and GLP-1RA in the preclinical setting results in beta-cell proliferation, islet neogenesis, and inhibition of beta-cell apoptosis in (human) cell lines.

Effects of Exenatide on Measures of β-Cell Function After 3 Years in Metformin-Treated Patients With Type 2 Diabetes

EXE and GLAR sustained HbA1c over the 3-year treatment period, while EXE reduced body weight and GLAR increased body weight. Following the 3-year treatment with EXE, the DI was sustained after a 4-week off-drug period. These findings suggest a beneficial effect on beta-cell health.

The current 3-year treatment data show a small but statistically significant effect on the DI following a 4-week off therapy period. Our results therefore suggest that a 3-year treatment with a GLP-1RA (such as EXE) is necessary to delineate an effect on beta-cell function.

Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years.

BACKGROUND:
Exenatide, an incretin mimetic for adjunctive treatment of type 2 diabetes (T2DM), reduced hemoglobin A(1c) (A1C) and weight in clinical trials. The objective of this study was to evaluate the effects of ≥ 3 years exenatide therapy on glycemic control, body weight, cardiometabolic markers, and safety.

CONCLUSION:
Adjunctive exenatide treatment for ≥ 3 years in T2DM patients resulted in sustained improvements in glycemic control, cardiovascular risk factors, and hepatic biomarkers, coupled with progressive weight reduction.

More than 3 years treatment of GLP-1 analogue resulted in sustained improvement.

Takes time to promote beta-cell proliferation and islet neogenesis from precursor cells in both in vivo and vitro models of diabetes.

Possible causes of early & delayed response

*Biology of incretins: GLP-1 and GIP*

Baggio LL, Drucker DJ.
metformin may enhance incretin signalling by increasing the plasma level of GLP-1 from L cells (red) but not GIP from K cells (blue), as well as by increasing the expression of GLP-1 and GIP receptors (GLP-1R and GIPR) in the insulin (yellow)-containing pancreatic beta cells via a PPARα-dependent mechanism.

**PPAR-α**: Peroxisome proliferator-activated receptor alpha
Gastric Cancer and bypass Surgery

Bypass surgery leaves blind segment of the stomach which are not readily accessible for either radiologic or endoscopic evaluation.

Screening and early detection is very important and critical for gastric cancer treatment
Preoperative evaluation of risk factors for developing cancer may lead to consideration of resection of the excluded stomach at time of RYGBP in selected patients, or the selection of other procedures in which endoscopic surveillance may be performed. Routine gastric resection in patients undergoing gastric bypass presents risks which likely outweigh the benefits.

This paper is from Chile, one of the leading epidemic area in the world.

Double balloon enterosocope

With sequential inflation and deflation of balloon with telescopic movement of two tubes, this scope can reach almost any part of the small intestine freely.
Access to the (bypassed) stomach after gastric bypass-Retrograde gastro-duodenoscopy with double balloon enteroscope
Options for possible gastric cancer in remnant stomach

1. Remove the remnant stomach: resectional gastric bypass

2. Transit bipartition

3. Double balloon enteroscope

4. Don’t mind

_Gastric Cancer after Roux-en-Y Gastric Bypass_

Alex Escalona, MD¹; Sergio Guzmán, MD¹; Luis Ibáñez, MD¹; Luis Meneses, MD²; Alvaro Huete, MD²; Antonieta Solar, MD³

Departments of ¹Digestive Surgery, ²Radiology and ³Pathology, Pontificia Universidad Católica de Chile, Santiago, Chile

Routine gastric resection in patients undergoing gastric bypass presents risks which likely outweigh the benefits.
The STAMPEDE trial randomized 60 subjects with uncontrolled type 2 diabetes to intensive medical therapy (IMT) alone, IMT + gastric bypass, or IMT + sleeve gastrectomy and followed these patients for 12 months.
1. Surgical intervention is most potent therapeutic modality to treat T2DM even in normal weight patients with enough evidence.

2. Surgical benefits should be weighed against risk. But with the patients with intractable T2DM, surgical intervention may be helpful.

3. Multidisciplinary approach can make complete remission and minimize complication.