Bariatric to metabolic surgery

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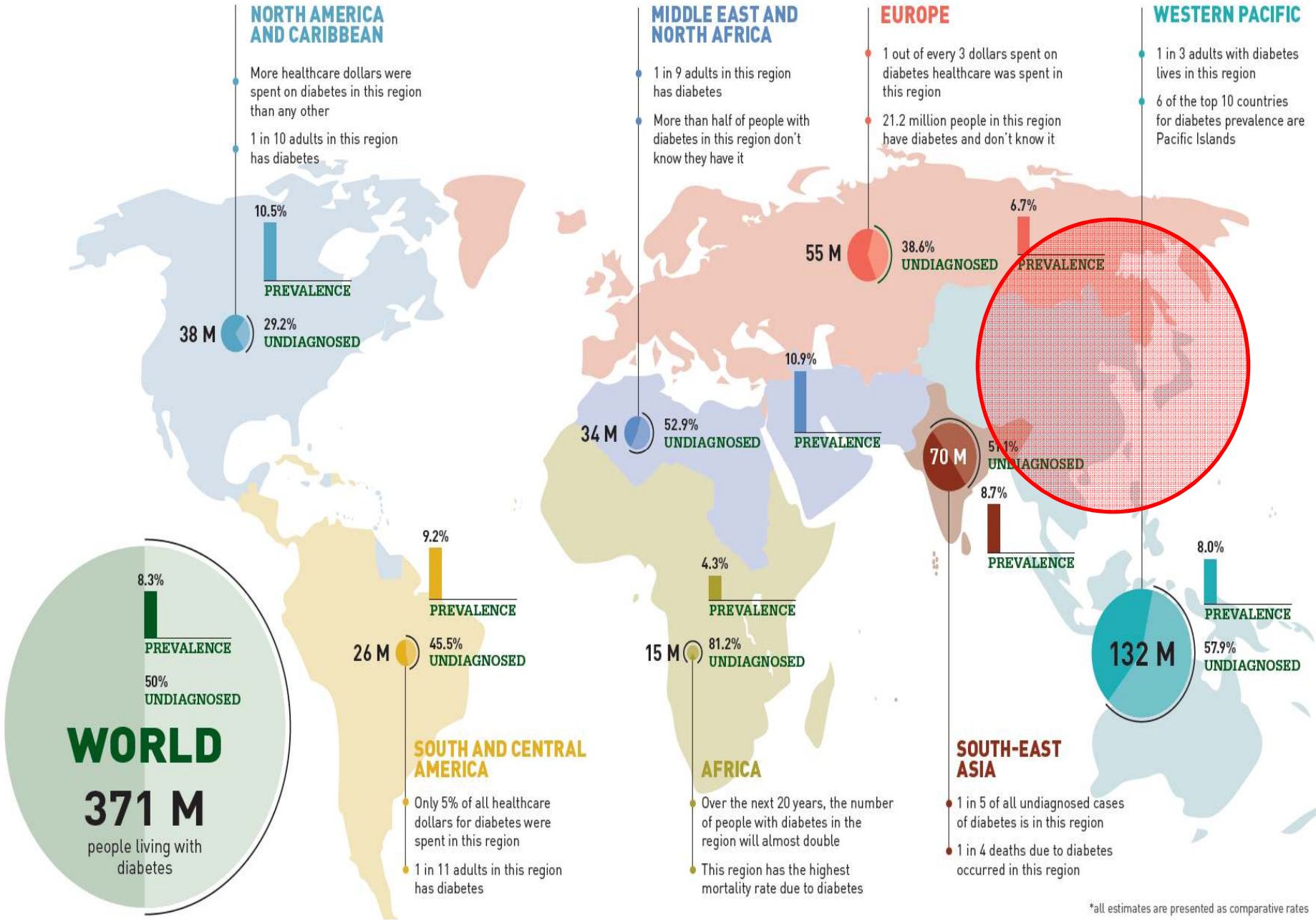
Seoul, Korea

International Diabetes Federation

IDF DIABETES ATLAS

5th edition | 2012 update



*all estimates are presented as comparative rates

Prevalence of Diabetes in Korea

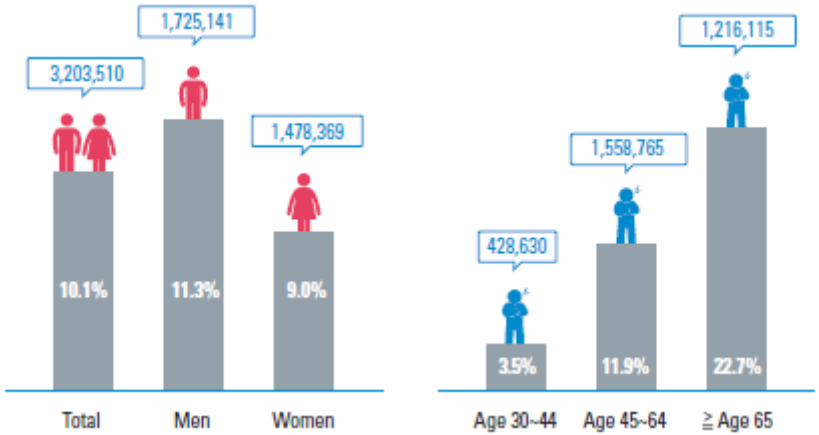
Prevalence : 10% + IGT : 20% = 30%

PREVALENCE OF DIABETES 2010 (≥ 30 YRS OLD)

성인당뇨병 유병률

3.2 Million

› 2010년 현재 30세 이상 당뇨병 유병률은 10.1%로 성인 10명 중 1명이 당뇨병환자 (약 320만명 추산).
› 연령이 높을수록 증가하여 65세 이상은 22.7%가 당뇨병환자.



IMPAIRED FASTING GLUCOSE (PREDIABETES)

공복혈당장애 (당뇨병 전단계)

6.2 Million

› 30세 이상 성인의 약 20%인 620만명이 공복혈당장애 (당뇨병 전단계).
› 따라서 2010년 현재 성인 10명 중 3명이 당뇨병환자 및 잠재적 당뇨병.

DIABETES FACT SHEET IN KOREA 2012

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

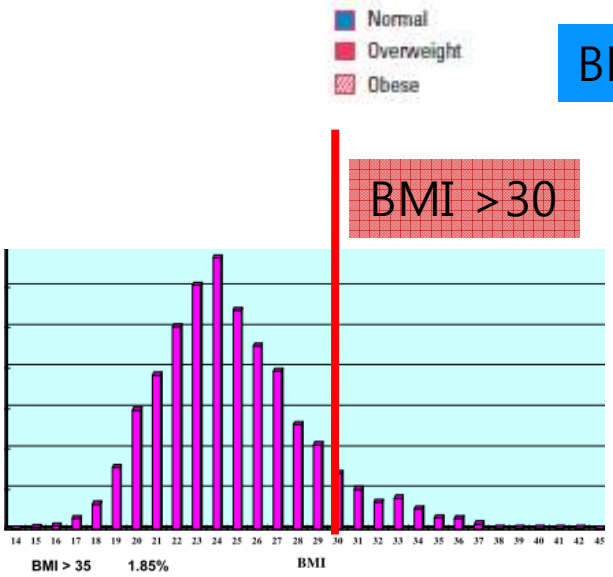
Korean has ethnical singularity of T2DM

	Korea	China	USA
DM	9.1%	9.3%	10.9%
Obesity (BMI > 30)	4.2%	4%	35%

DIABETES FACT SHEET IN KOREA 2012

BMI less than 25 kg/m^2 (50%)

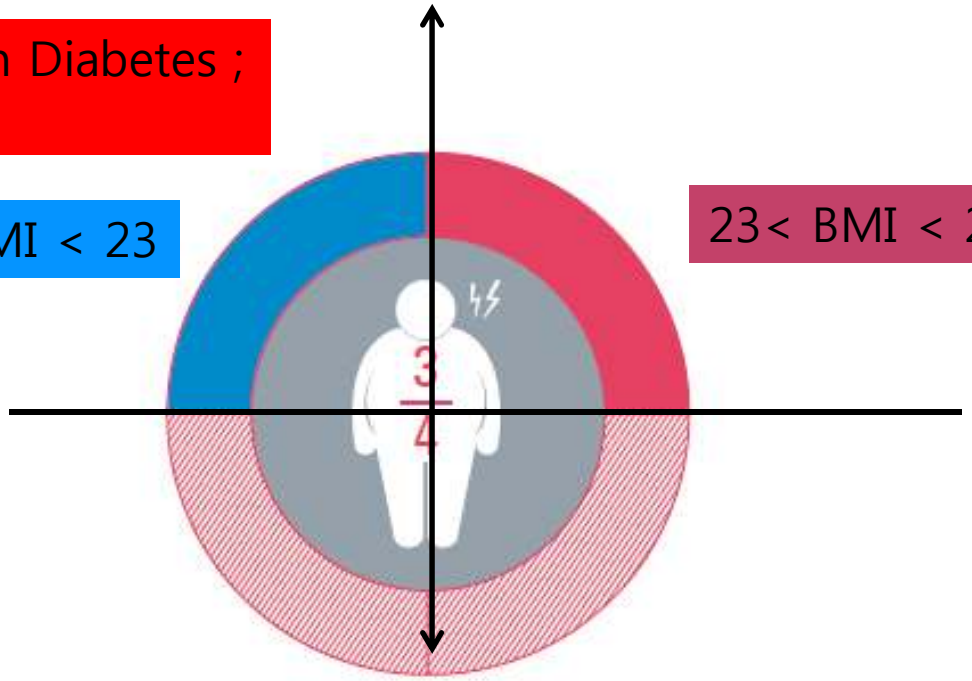
Mean BMI of Korean Diabetes ; 25.2 kg/m^2



BMI < 23

BMI >30

23< BMI < 24.9



BMI more than 25 kg/m^2

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

Korean type 2 diabetes has ethnical singularity

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)

Oh TJ, Kim MY, Shin JY, Lee JC, Kim SCho YM.
*The **incretin effect** in **Korean subjects** with **normal glucose tolerance** or **type 2** diabetes.*
Clin Endocrinol (Oxf). 2013 Feb 13.

Metabolic surgery for T2DM
with low body mass index
and impaired pancreatic function

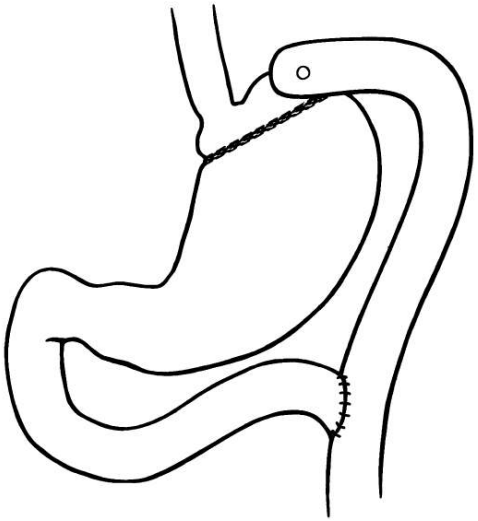
ANNALS OF SURGERY
Vol. 222, No. 3, 339–352

Who Would Have Thought It?

An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus

Walter J. Pories, M.D., Melvin S. Swanson, Ph.D., Kenneth G. MacDonald, M.D., Stuart B. Long, B.S., Patricia G. Morris, B.S.N., Brenda M. Brown, M.R.A., Hisham A. Barakat, Ph.D., Richard A. deRamon, M.D., Gay Israel, Ed.D., Jeanette M. Dolezal, Ph.D., and Lynis Dohm, Ph.D.

From the Departments of Surgery and Biochemistry of the School of Medicine and the Performance Laboratory of East Carolina University, Greenville, North Carolina



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**.

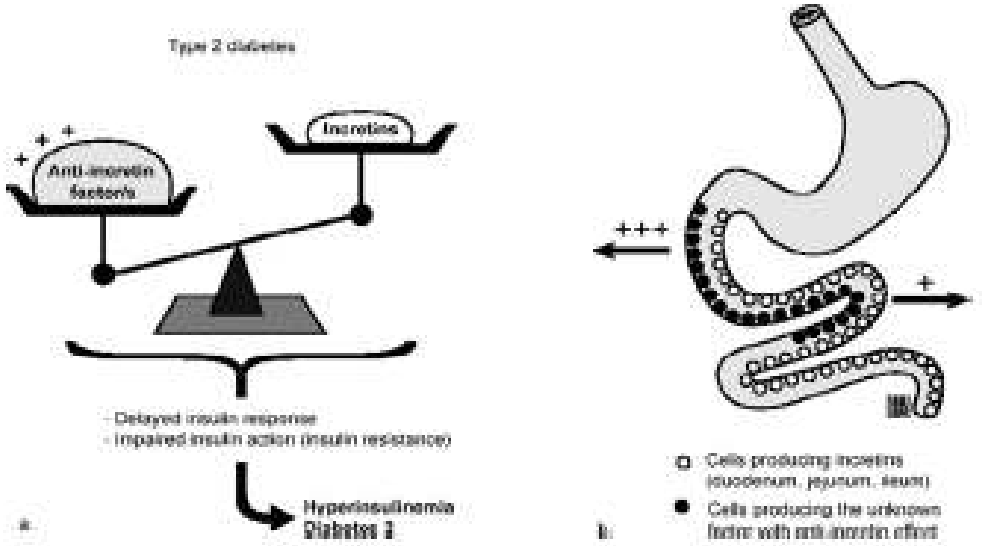
Why the operation controls **diabetes so well is not clear**, but the major reason appears to be the reduction of caloric intake. There is some evidence that changes in the **incretin** stimulation of the islets by the gut may also play a role.

Incretin may have a role to control DM

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

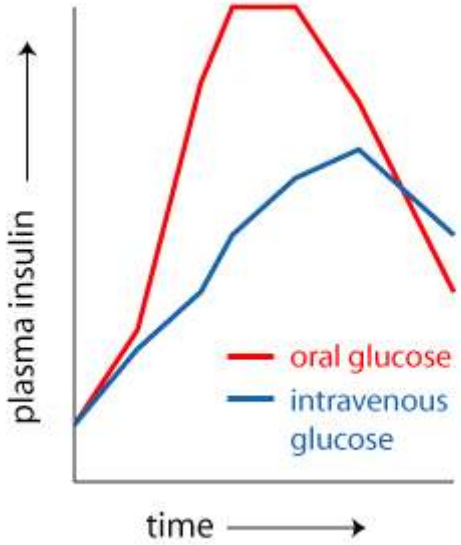
Foregut has a role for development of T2DM
But didn't know exactly.

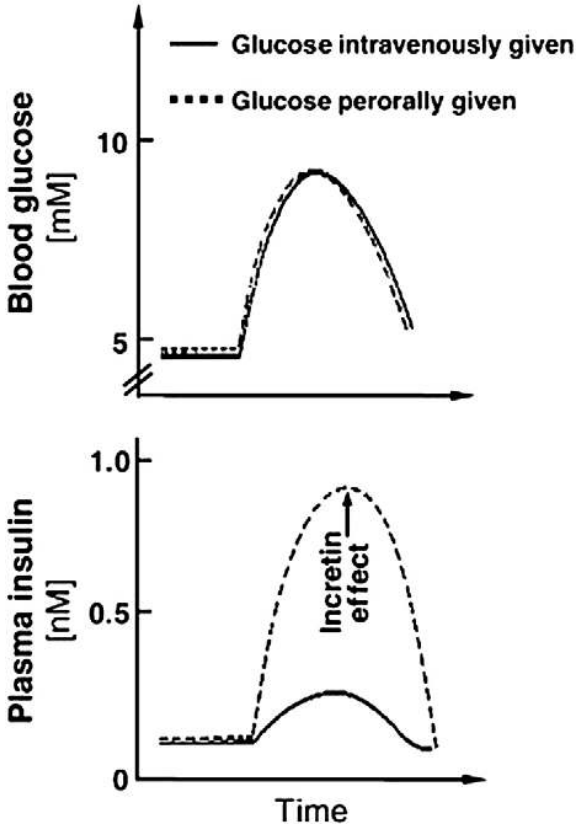
Anyway They opened the possibility of surgical treatment for non obese T2DM.



*The **mechanism** of **diabetes control after gastrointestinal bypass surgery** reveals a role of the proximal small intestine in the pathophysiology of type 2 **diabetes**.*
Rubino F, Forgione A, Cummings DE, Vix M, Gnuli D, Mingrone G, Castagneto M, Marescaux J.
Ann Surg. 2006 Nov;244(5):741-9

The incretin is very important to glucose metabolism





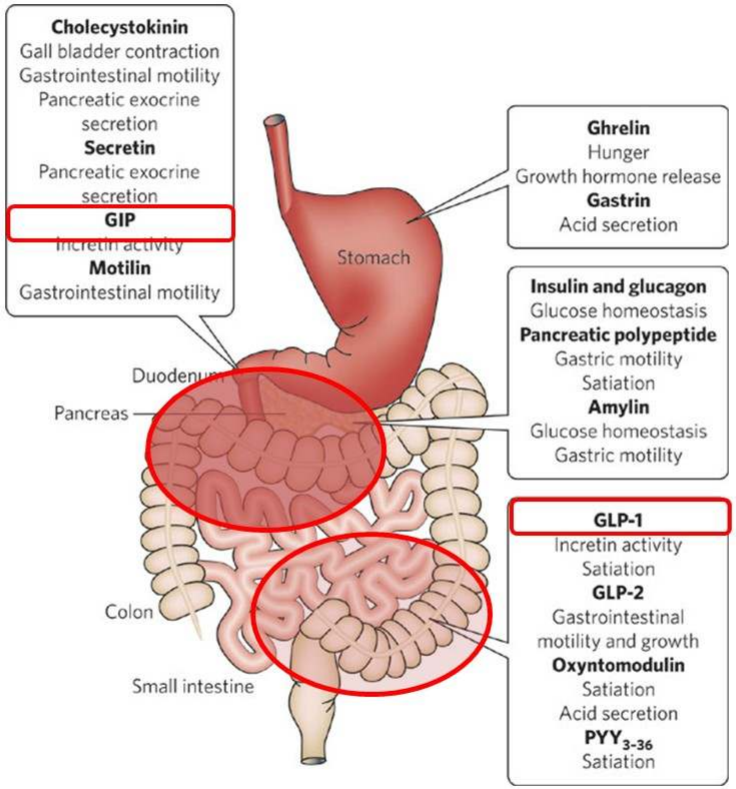
Incretin effect is increased secretion of insulin when glucose is taken orally than to infused ntravenously.

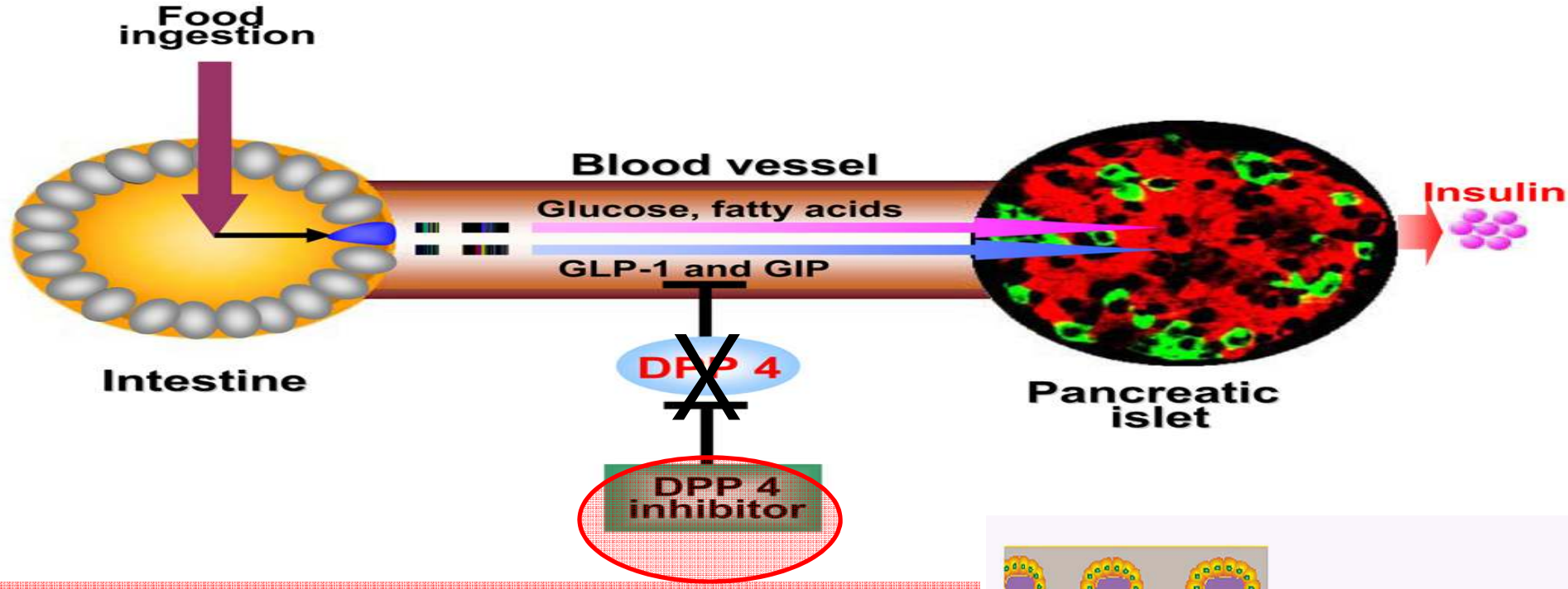
An estimated 50–70% of insulin secretion after glucose ingestion is attributable to this observation, which is now known as the 'incretin effect'.

The incretin

***Biology** of **incretins**: **GLP-1** and **GIP**.*
*Baggio LL, **Drucker** DJ.*
Gastroenterology. 2007 May;132(6):2131-57.

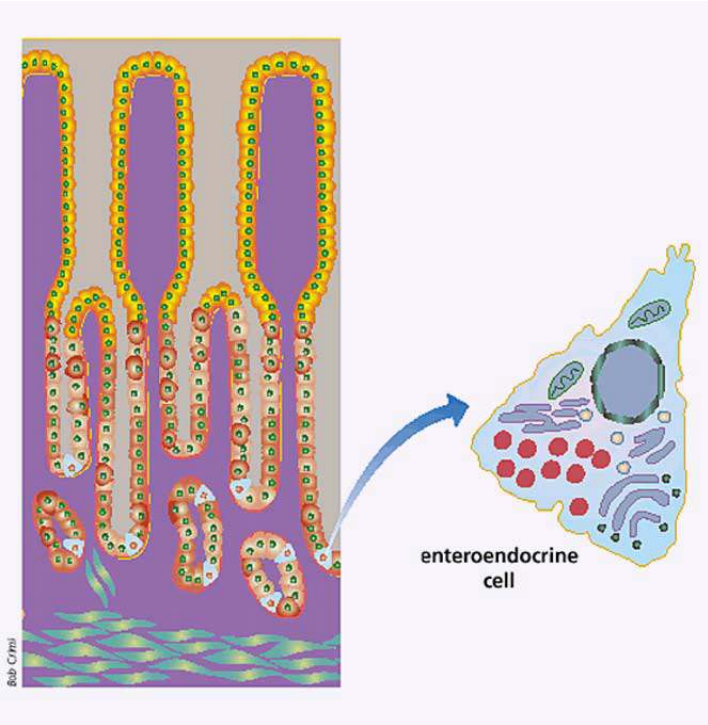
GIP and GLP-1 are the only incretin hormone in humans.
Furthermore, studies have shown that these 2 peptides potentiate glucose stimulated insulin secretion in an additive manner, likely contribute equally to the incretin effect, and together can fully account for the incretin effect in humans.





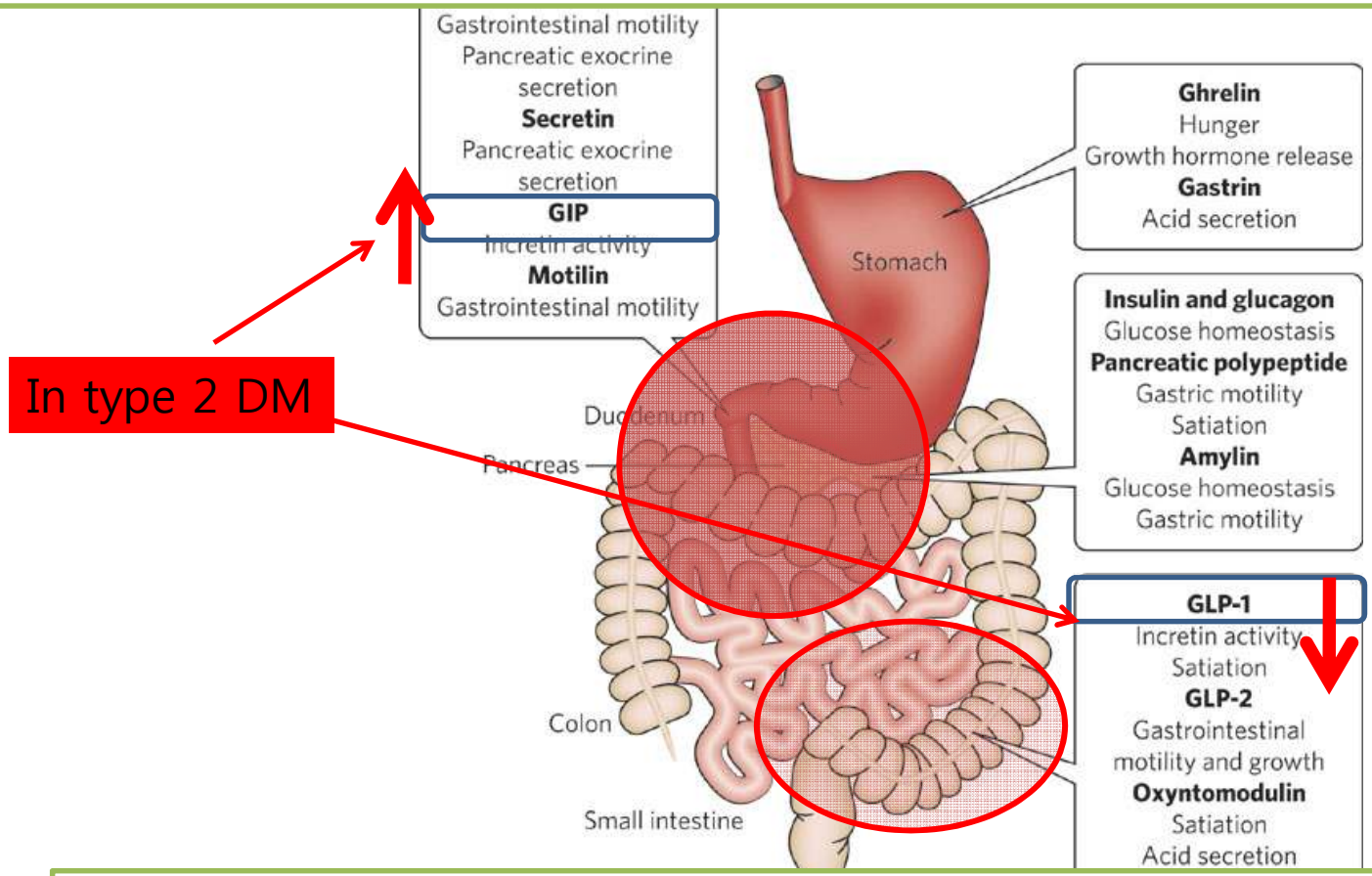
Nutrient in the bowel lumen stimulate enteroendocrine cells. (secretion is made by in response to nutrient ,not food residue)
They have strong inotropic effect to insulin secretion.
But this action was deactivated by DPP4.

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



Healthy subjects Vs Type 2 diabetic patients

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



Concentration of GLP-1 decreased but insulinotropic action is preserved.

These altered secretion of incretin is closely related to the cause of T2DM

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

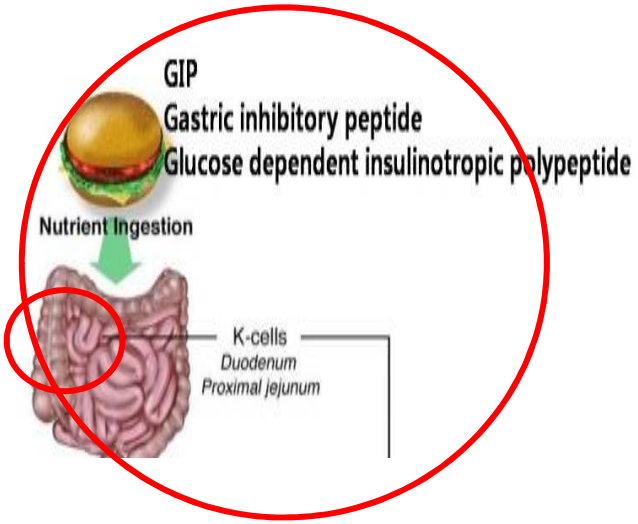
Not due to amount of food
But due to eating habit

Higher glycemic index, and
Glycemic load value.

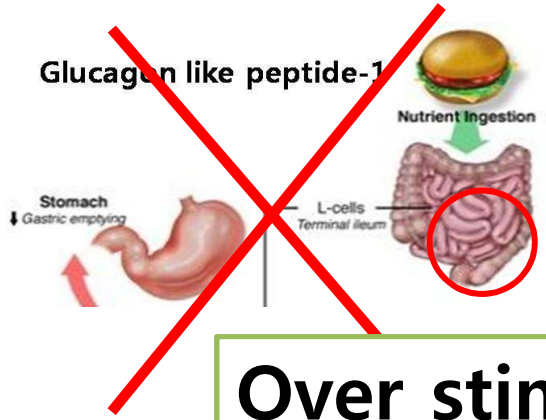
Polished rice, refined wheat

Chan JC et al. JAMA. 2009 May 27;301(20):2129-40.
Diabetes in Asia: epidemiology, risk factors, and pathophysiology.

High GI & Incretin



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.

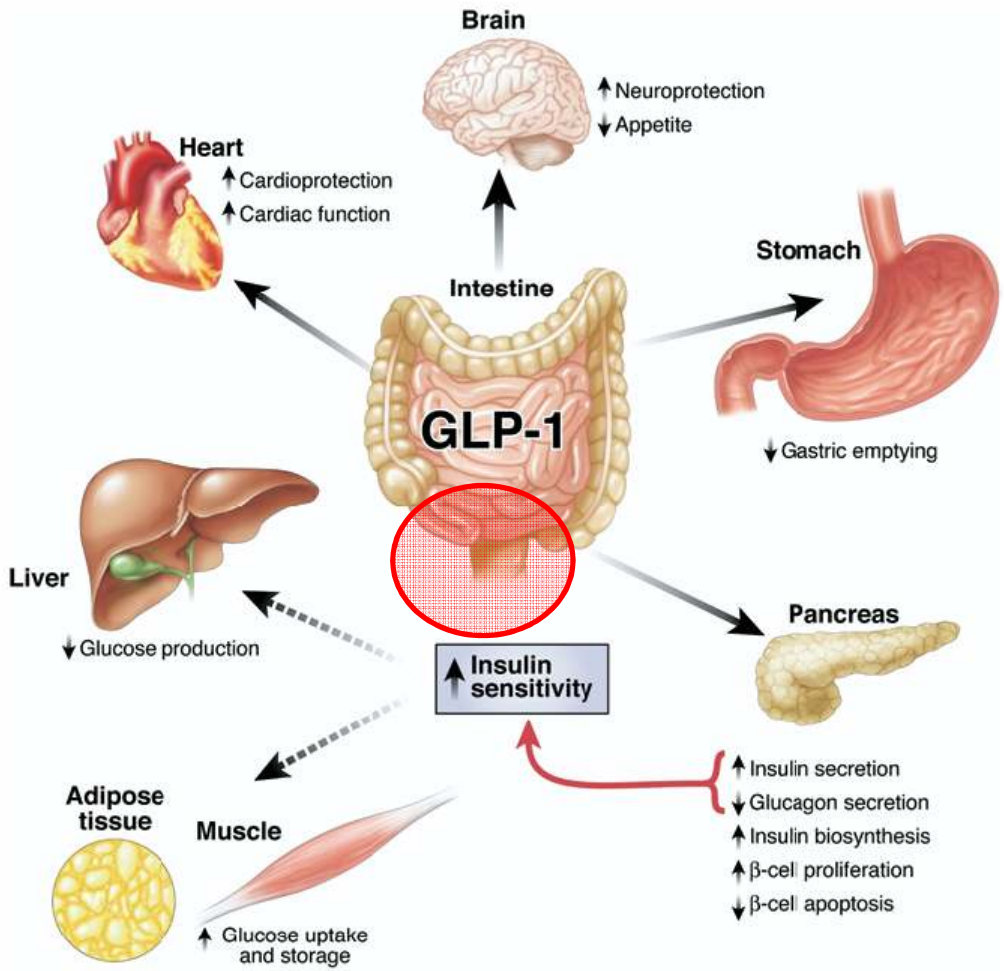
Over stimulation of foregut from nutrient

Exhaustion of nutrient to stimulate distal gut

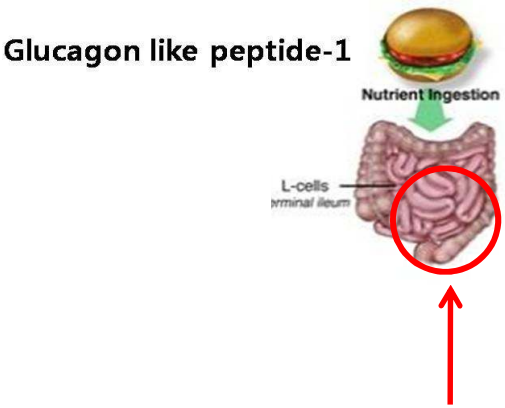
Sleeve gastrectomy with transit bipartition: a potent interv ention for metabolic syndrome and obesity. Santoro S, Castro LC, Velhote MC, Malzoni CE, Klajner S, Castro LP, Lacombe A, Santo MA.Ann Surg. 2012 Jul;256(1):104-10.

The pathophysiologic function of GLP-1 and GIP

GLP-1 actions in peripheral tissues



*Biology of **incretins**: GLP-1 and GIP.*
***Baggio** LL, Drucker DJ.*
Gastroenterology. 2007 May;132(6):2131-57. Review.



Released in response to
Nutrient in Distal gut

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

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

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)

novo nordisk®

LAPS-Exendin
(long acting GLP-1 agonist, 1/month)

Incretin based treatment is more effective to Korean diabetic subjects

Diabetologia (2013) 56:696–708
DOI 10.1007/s00125-012-2827-3

META-ANALYSIS

Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis

Y. G. Kim · S. Hahn · T. J. Oh · S. H. Kwak · K. S. Park · Y. M. Cho

*Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. **Differences** in the **glucose-lowering efficacy** of **dipeptidyl peptidase-4** inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia. 2013 Apr;56(4):696-708.*

Original Article
Clinical Care/Education
Diabetes Metab J 2012;36:364-370
http://dx.doi.org/10.4093/dmj.2012.36.5.364
pISSN 2233-6079 · eISSN 2233-6087

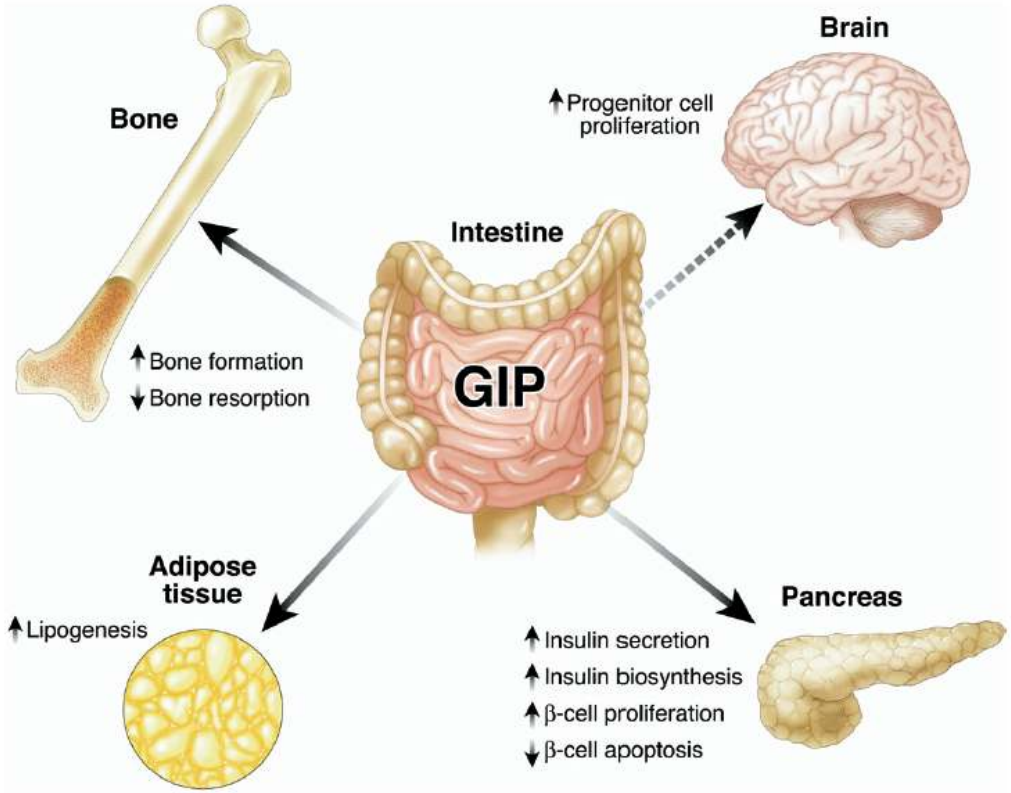
dmj
DIABETES & METABOLISM JOURNAL

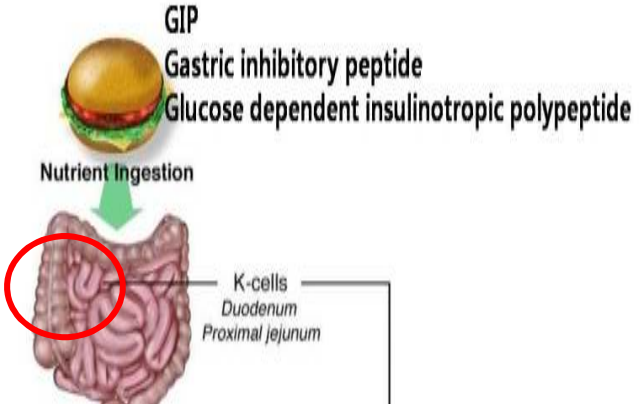
Effects of a 6-Month Exenatide Therapy on HbA1c and Weight in Korean Patients with Type 2 Diabetes: A Retrospective Cohort Study

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*

GIP actions in peripheral tissues





Released in response to
Nutrient in proximal gut

*Biology of **incretins**: GLP-1 and GIP.*
***Baggio** LL, Drucker DJ.*
Gastroenterology. 2007 May;132(6):2131-57. Review.

Healthy subject, the GIP is insulinotropic hormone
but in hyperglycemia, insulinotropic action is attenuated.
Big problem of GIP **is functional diversity.**

GIP is unpredictable

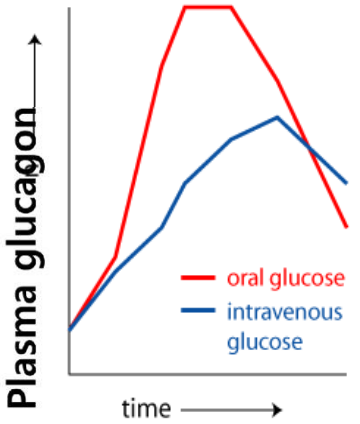
Interfering the suppression of
Postprandial glucagon release

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



Patients with T2DM

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.

Diabetologia. 2007 Apr;50(4):797-805. Epub 2007 Jan 16.
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.

Role of GIP to glucagon in T2DM

In type 2 diabetes, the postprandial glucagon suppression is attenuated

The separate and combined impact of the intestinal hormones, GIP, GLP-1, and GLP-2, on glucagon secretion in type 2 diabetes

Asger Lund, Tina Vilsbøll, Jonatan I. Bagger, Jens J. Holst and Filip K. Knop

Am J Physiol Endocrinol Metab 300:E1038-E1046, 2011. First published 8 March 2011;
doi: 10.1152/ajpendo.00665.2010

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.

*Lund A, Vilsbøll T, Bagger JI, Holst JJ, Knop FK. The **separate** and **combined impact** of the **intestinal hormones**, GIP, GLP-1, and GLP-2, on glucagon secretion in type 2 diabetes.*
Am J Physiol Endocrinol Metab. 2011 Jun;300(6):E1038-46.

Role of GIP in T2DM

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

Nikolaos Mentis,[1] Irfan Vardarli,[1] Lars D. Köthe,[1] Jens J. Holst,[2] Carolyn F. Deacon,[2] Michael Theodorakis,[3] Juris J. Meier,[4] and Michael A. Nauck[1]

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**

Mentis N, Vardarli I, Köthe LD, Holst JJ, Deacon CF, Theodorakis M, Meier JJ, Nauck MA.
GIP does not potentiate the antidiabetic effects of GLP-1 in hyperglycemic patients with type 2 diabetes.
Diabetes. 2011 Apr;60(4):1270-6.

Role of GIP to glucagon in T2DM

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

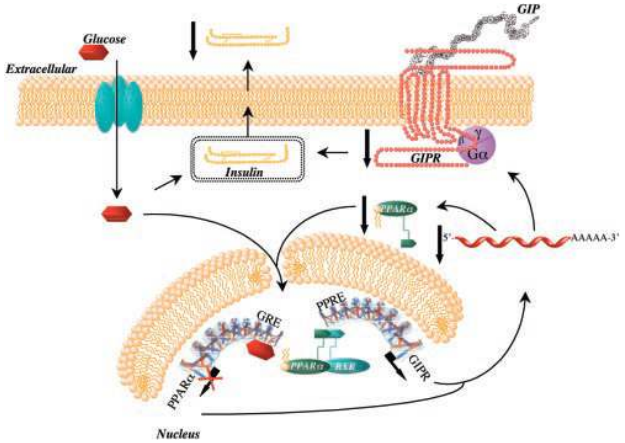
Chia CW, Carlson OD, Kim W, Shin YK, Charles CP, Kim HS, Melvin DL, Egan JM. ***Exogenous glucose-dependent insulinotropic polypeptide worsens post prandial hyperglycemia in type 2 diabetes.*** *Diabetes. 2009 Jun;58(6):1342-9.*

GIP receptor downregulation in T2DM

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).

*Cho YM, Merchant CE, Kieffer TJ. **Targeting** the **gluca gon receptor family** for **diabetes** and **obesity thera py**. Pharmacol Ther. 2012 Sep;135(3):247-78.*

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.



Reduction of PPAR α transcription

Lynn FC, Thompson SA, Pospisilik JA, Ehses JA, Hinke SA, Pamir N, McIntosh CH, Pederson RA.
A novel pathway for regulation of glucose-dependent insuli notropic polypeptide (GIP) receptor expression in beta cells.
FASEB J. 2003 Jan;17(1):91-3.

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

Therapeutic potential for GIP receptor agonists and antagonists

Nigel Irwin, PhD, Research Fellow *, Peter R. Flatt, Professor

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

Irwin N, Flatt PR Best Pract Res Clin Endocrinol Metab.
Therapeutic potential for GIP receptor agonists and antagonists. *2009 Aug;23(4):499-512.*

Review

Mining incretin hormone pathways for novel therapies

Rhonda D. Wideman[1] and Timothy J. Kieffer[1,2]

[1] Laboratory of Molecular and Cellular Medicine, Department of Cellular and Physiological Sciences, Life Sciences Institute, University of British Columbia, 2350 Health Sciences Mall, Vancouver, British Columbia, V6T 1Z3, Canada
[2] Department of Surgery, University of British Columbia, Vancouver, British Columbia, V5Z 4E3, Canada

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.

Wideman RD, Kieffer TJ.
Mining incretin hormone pathways for novel therapies.
Trends Endocrinol Metab. 2009 Aug;20(6):280-6.

Summary of limitations of medical treatment (Incretin based treatment)

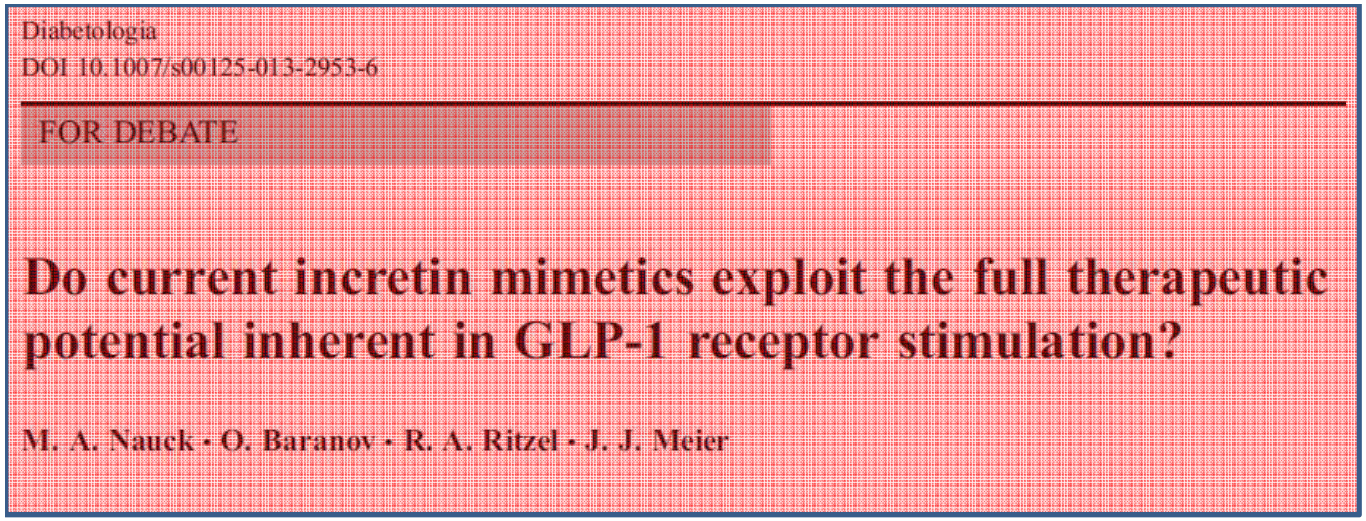
Side effect of GLP-1 analogue

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?*
Nauck MA, Baranov O, Ritzel RA, Meier JJ.
Diabetologia. 2013 Jun 8.

TIME Healthland

A Healthy Balance of the Mind, Body and Spirit

DIABETES

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

The NEW ENGLAND JOURNAL of MEDICINE

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Cleveland group

Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

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Medical Tx. Vs Sleeve Gastrectomy vs RnY GBP

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Italian group

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

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Medical Tx. vs RnY GBP vs BPD

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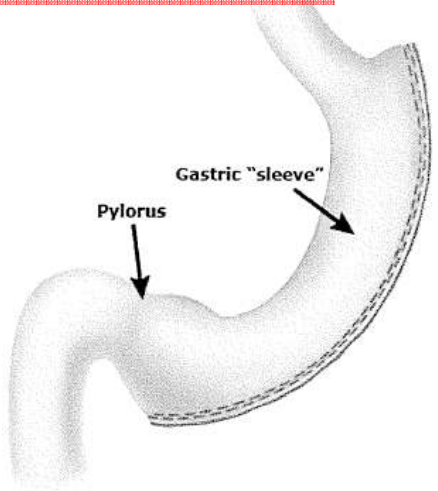
Effect of glycemic control

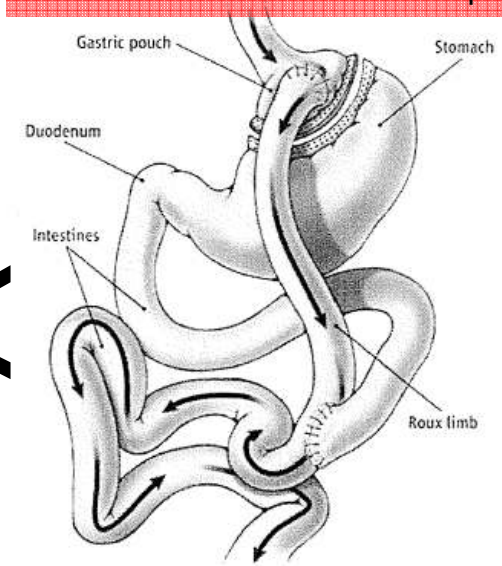
Purely restrictive



Sleeve gastrectomy

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

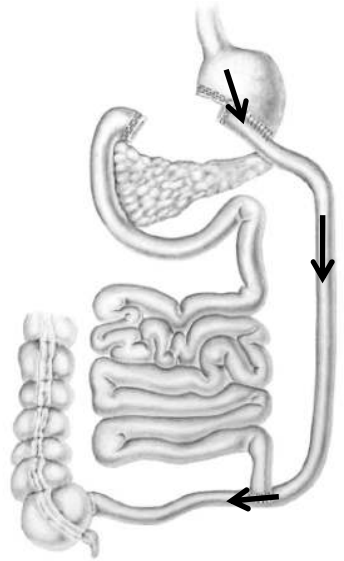
Restrictive > mal-absorptive



RnY Gastric bypass

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

Purely mal-absorptive



BPD
(Bilio-pancreatic diversion)

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

Mingrone G.
Nutr Metab Cardiovasc Dis. 2008 Oct;18(8):574-9.

Glycatyed Hb<6.5%
Without medication

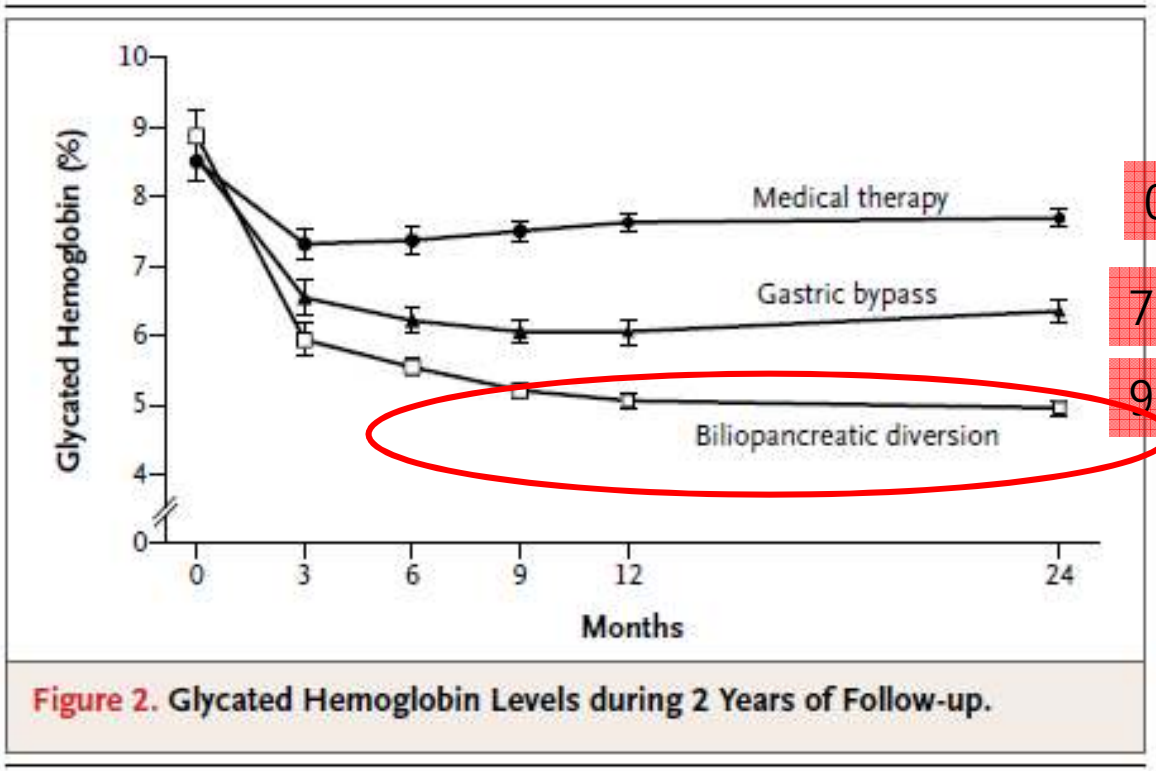


Figure 2. Glycated Hemoglobin Levels during 2 Years of Follow-up.

0%

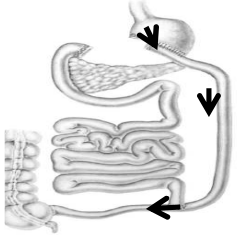
75%

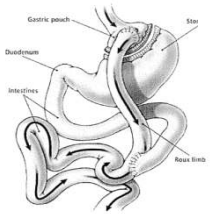
95%

Biliopancreatic diversion > gastric bypass > Sleeve gastrectomy > Medical Tx

Table 2 Mechanisms of action of bariatric surgery in improving/reverting type 2 diabetes mellitus

Biliopancreatic diversion
Purely mal-absorptive

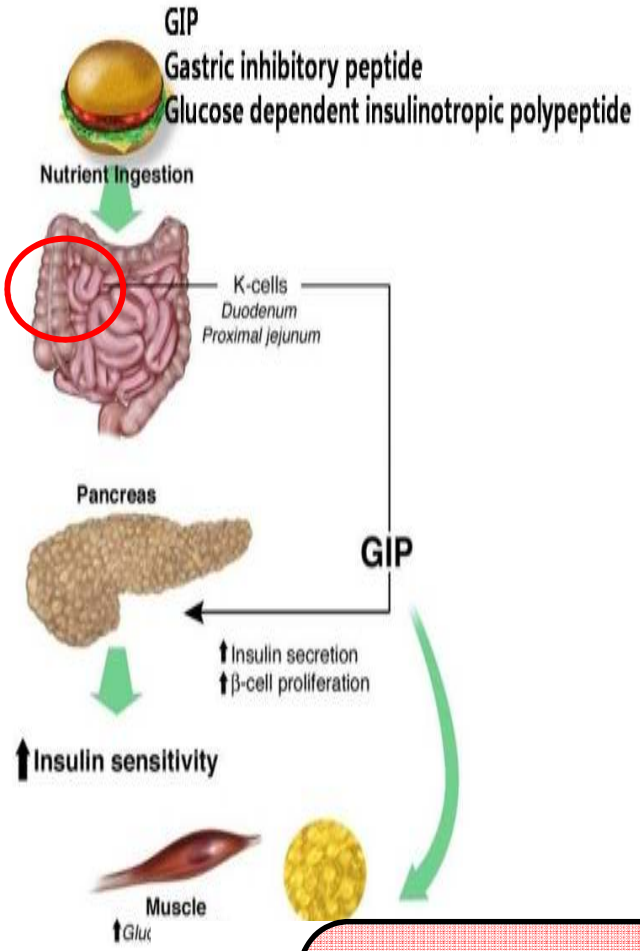




RnY procedure
Restrictive > mal-absorptive

Diabetes resolution (%)	98.9	83.7	[23]
Insulin sensitivity restoration (euglycemic hyperinsulinemic clamp)	Normal Supranormal	Unchanged Slightly improved	[42] [43] [49] [50]
Insulin secretion after OGTT or a meal	Reduced	Increased	[43,39]
GIP secretion after OGTT or a meal	Reduced	Increased	[34,39]
GLP-1 secretion after OGTT or a meal	Increased	Increased	[34,39]

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



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.

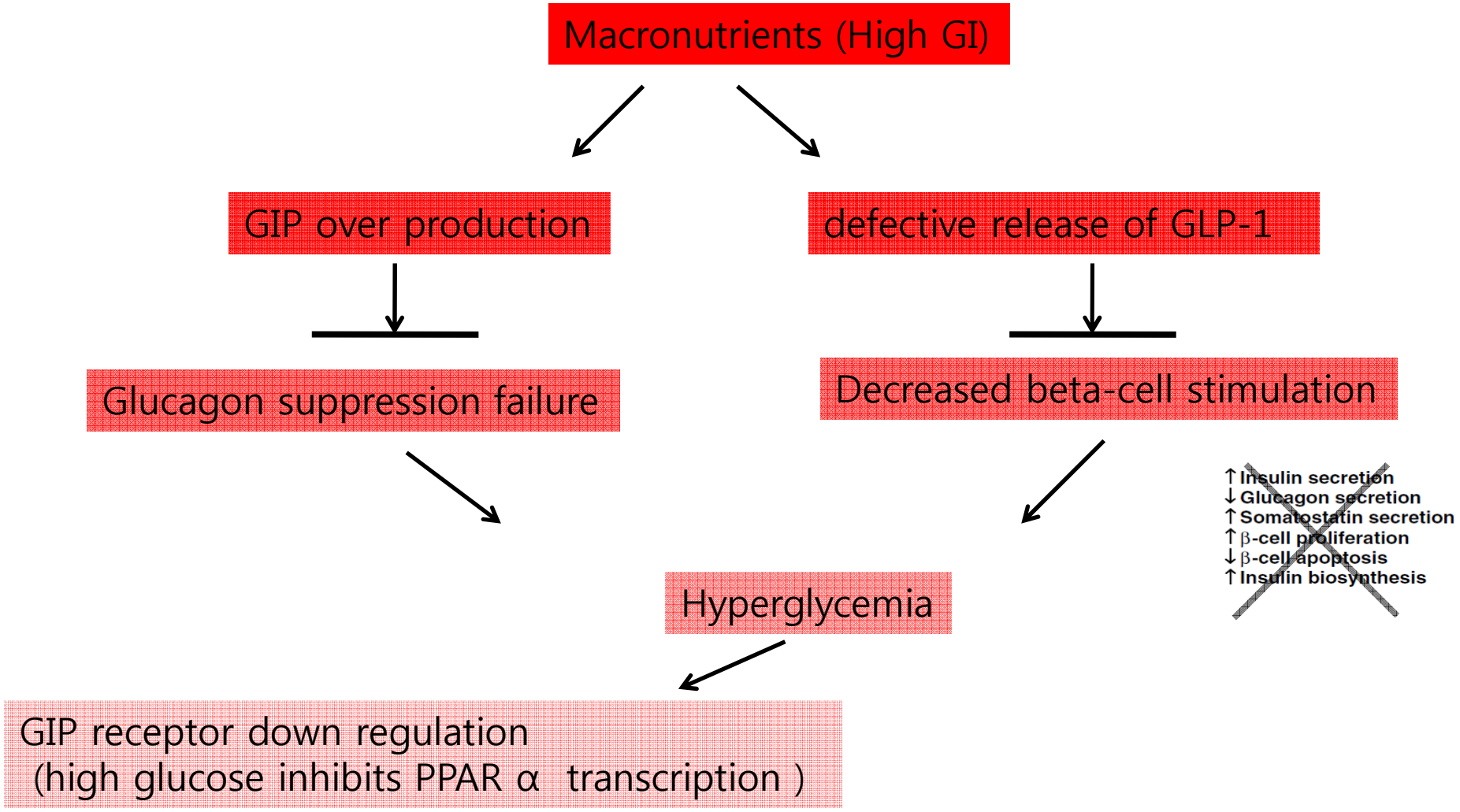
Glucose-dependent insulinotropic polypeptide (GIP) is a hormone mainly produced in the proximal segments of bowel. It has been shown that GIP is overproduced in patients with obesity and T2DM, whereas the production of GLP-1 deficiency was also demonstrated in patients with type 2 diabetes

Santoro S et al.
Ann Surg. 2012 Jul;256(1):104-10.

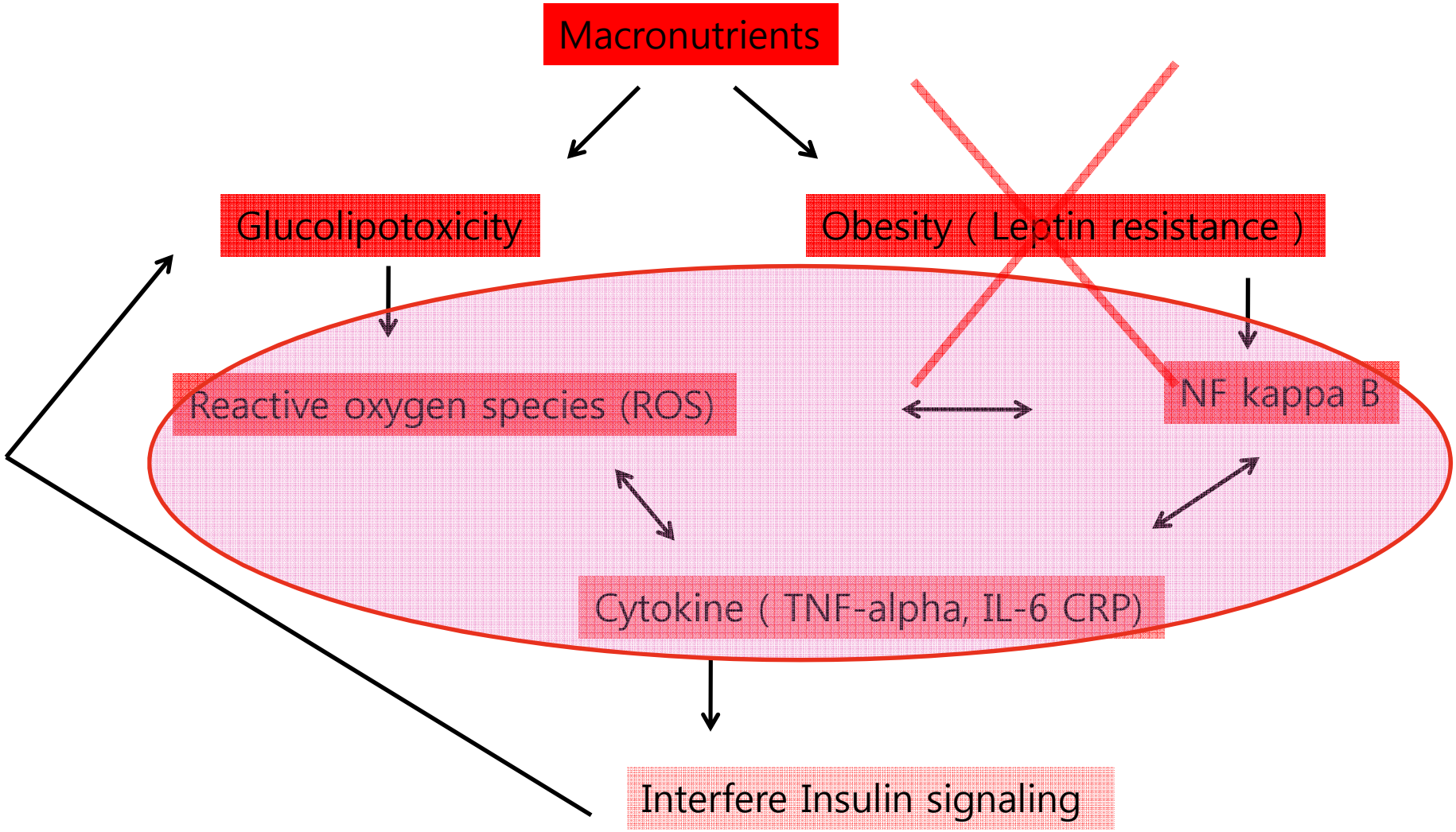
Part of the results observed after BPD can be attained by the reduction of circulating levels of GIP and the simultaneous increase of plasma GLP-1 concentration.

Mingrone G. ***Role of the incretin system in the remission of type 2 diabetes following bariatric surgery.*** *Nutr Metab Cardiovasc Dis. 2008 Oct;18(8):574-9.*

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

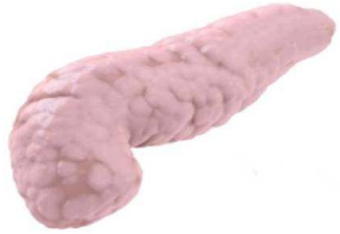


Pathogenesis of T2DM (inflammantion)
2.Peripheral resistance to insulin



Following insulin resistance will be corrected with euglycemia because the patient dose 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



↑Insulin secretion
↓Glucagon secretion
↑Somatostatin secretion
↑β-cell proliferation
↓β-cell apoptosis
↑Insulin biosynthesis

Surgical mechanism of diabetic control

Caloric Restriction

Changes in adipoinsular axis

Changes in enteroinsular axis

→ GIP↓ GLP-1↑

Personal experience of metabolic surgery

International Diabetes Federation

Most important strategy for 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

International Diabetes Federation

Most important strategy for surgery

Why the simplicity and reversibility

Sugery 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 lot 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 hypotheis is

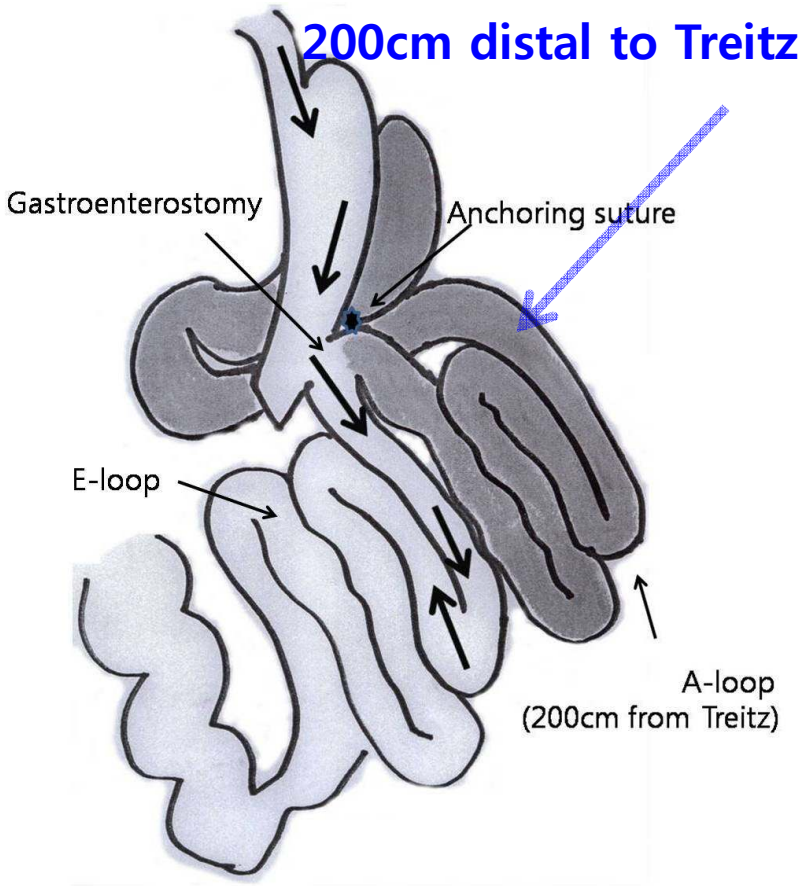
Loss or impaired and imbalanced incretin effect is major problem in Korean Diabetic Pt.

Single anastomosis gastric bypass with long afferent loop would be effective to normalize entero-insular axis.

Surgery

Long vertical gastric tube is made along the lesser curvature from 2cm proximal to the pylorus aiming the fundus.

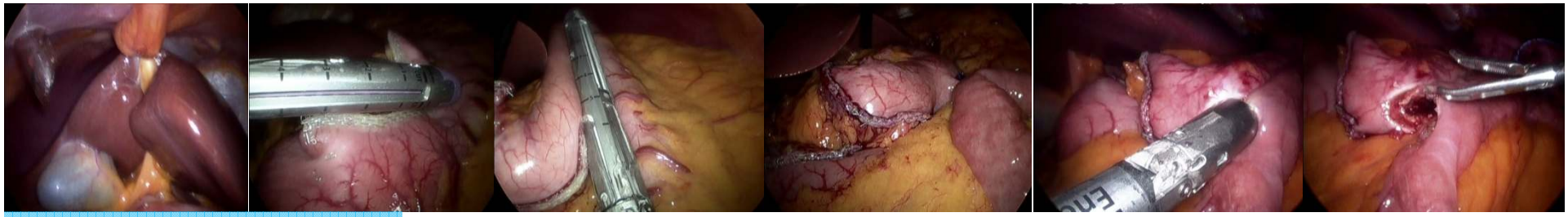
And small Intestine, 200cm distal to Treitz ligament, is bypassed through single anasotmosis.



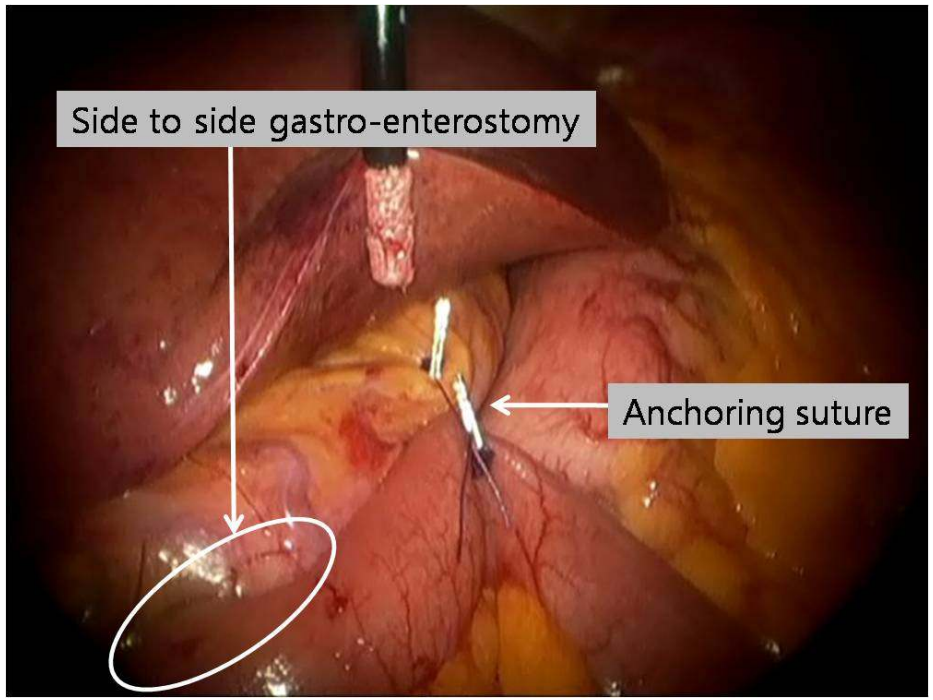
Simple, easy → **Safety , easy reversibility**

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

Complete exclusion of foregut From nutrient to release GIP



Our experience



The anasotmosis 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

Our experience

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/m^2)
- 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

Asian Journal of Surgery (2013) xx, 1–8

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journal homepage: www.e-asianjournalsurgery.com

ORIGINAL ARTICLE

Incretin levels 1 month after laparoscopic single anastomosis gastric bypass surgery in non-morbid obese type 2 diabetes patients

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Received 24 April 2013; received in revised form 13 September 2013; accepted 23 September 2013

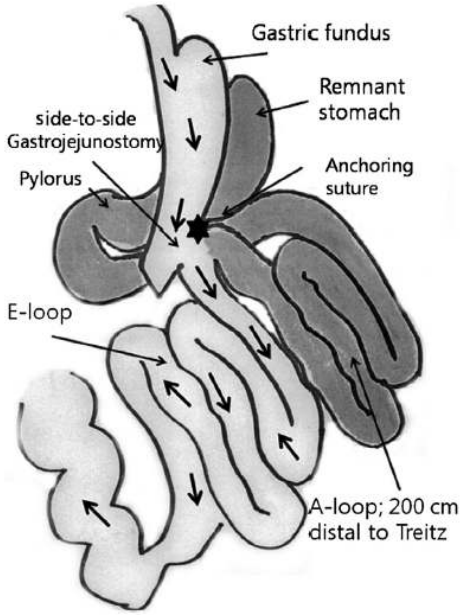
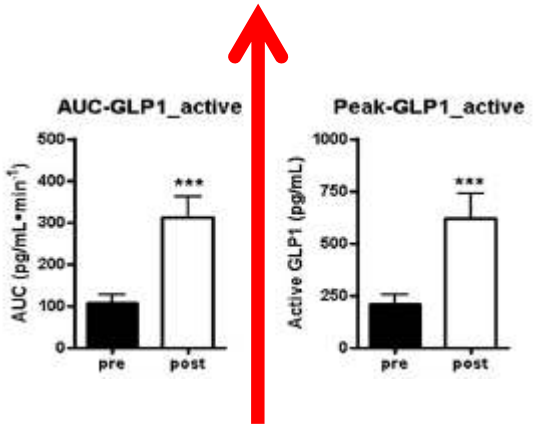
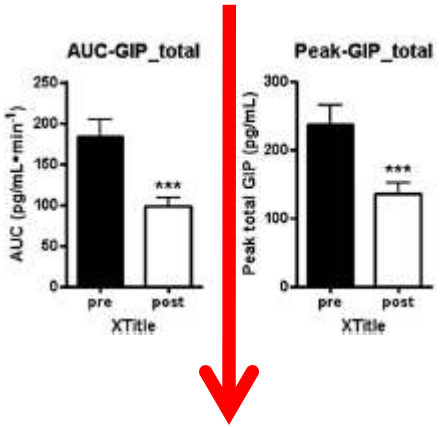


Figure 1 Illustration of single anastomosis gastric bypass surgery. The surgeon made a vertical gastric tube and anastomosed it with jejunum 200 cm distal from the ligament of Treitz.



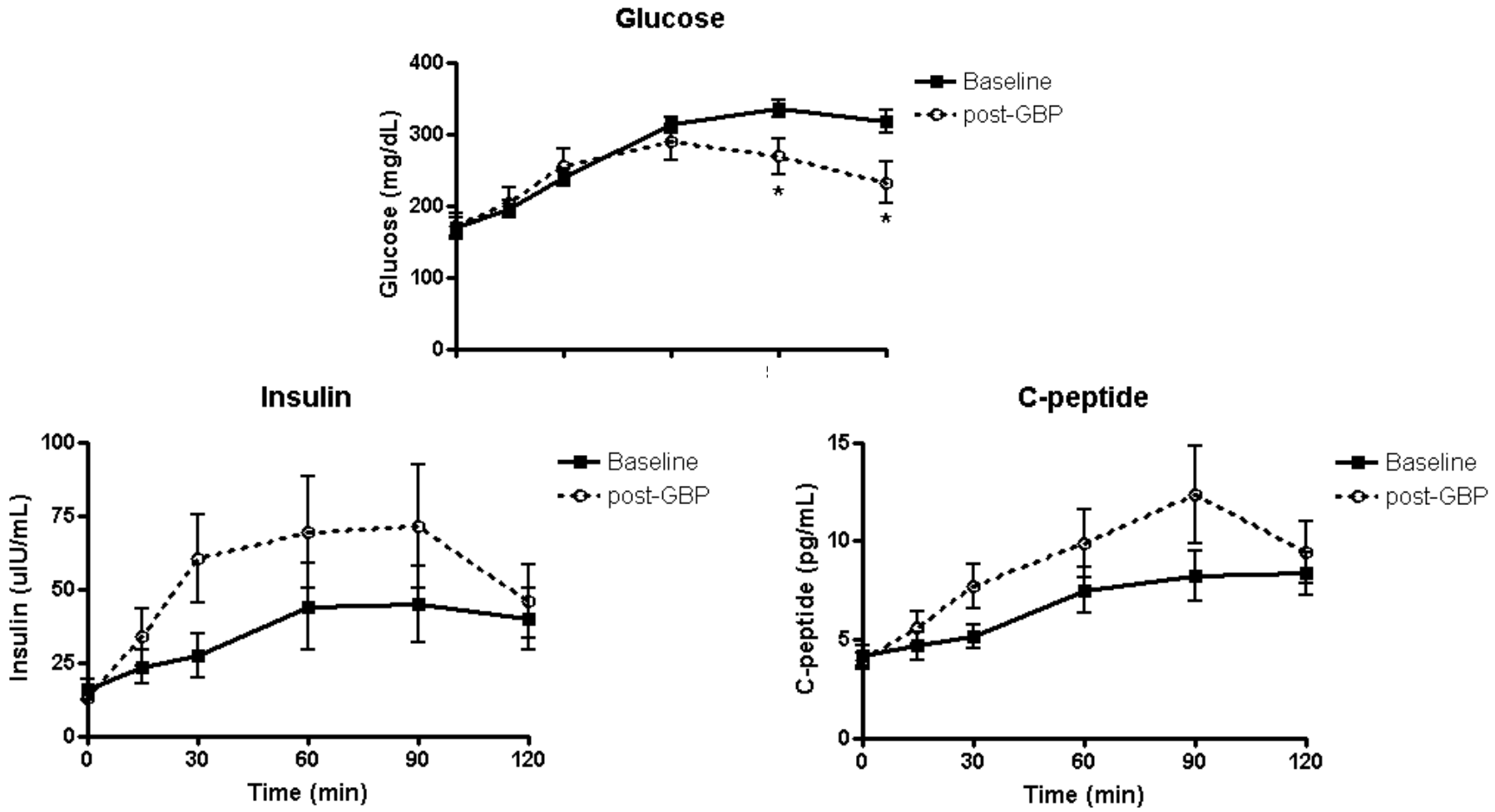
GLP-1

GIP



Our experience

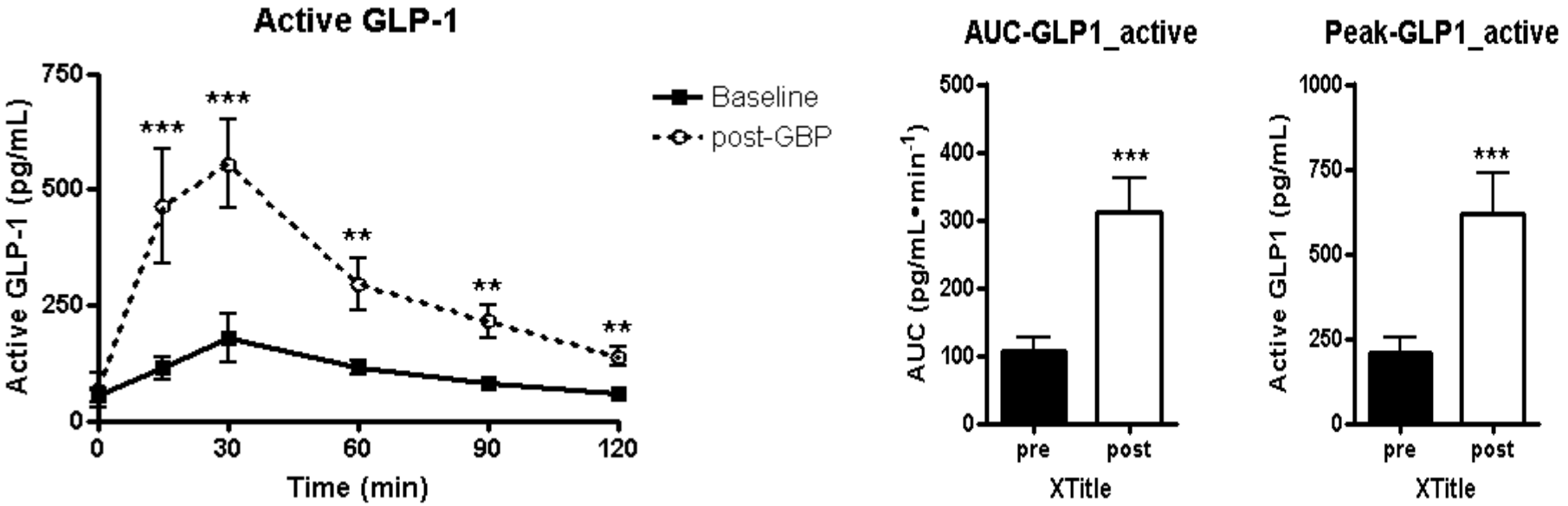
Glucose,Insulin, c-peptide



AUC of Insulin and c-peptide increased AUC of glucose was decreased

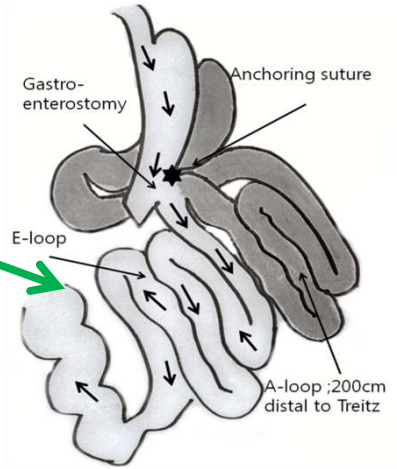
Our experience

Active GLP-1 of OGTT



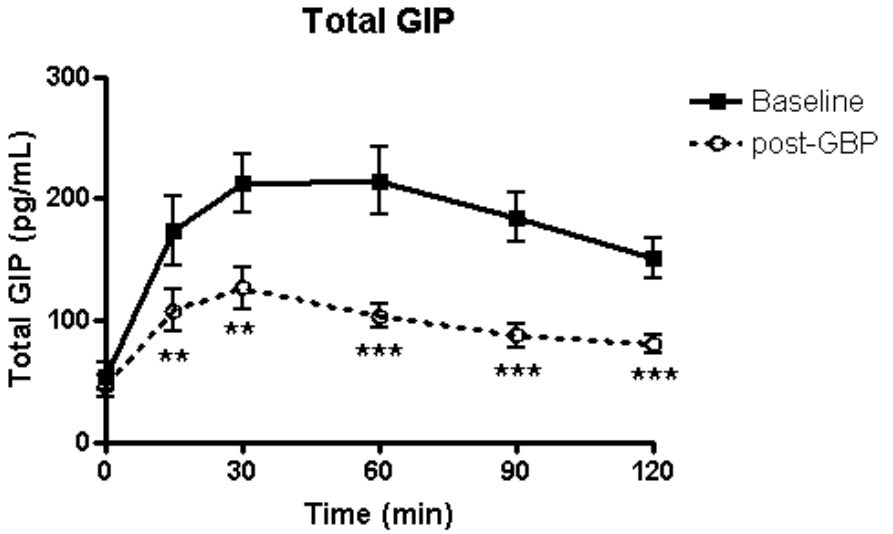
Peak level & AUC was increased markedly

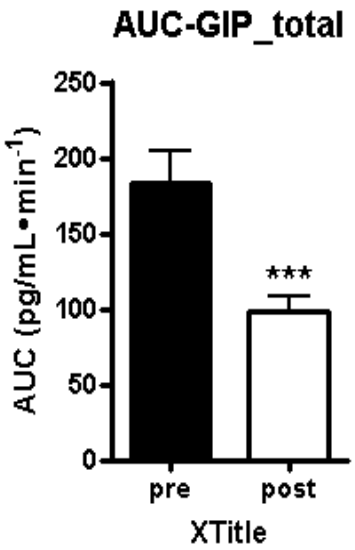
Expedited delivery of nutrient
To distal small bowel stimulate
L-cell

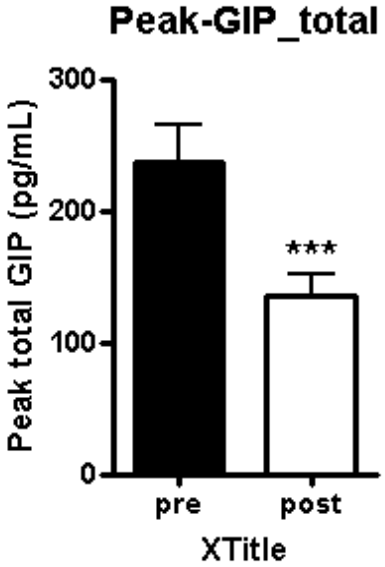


Our experience

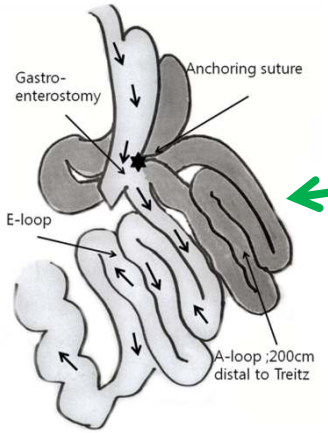
Total GIP







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

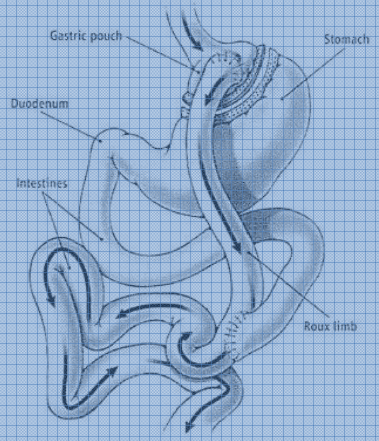
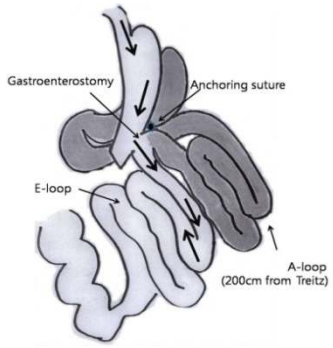


Figure from ***Mingrone*** *G. Insulin sensitivity and secretion modifications after bariatric surgery. J Endocrinol Invest. 2012 Jul;35(7):692-8.*

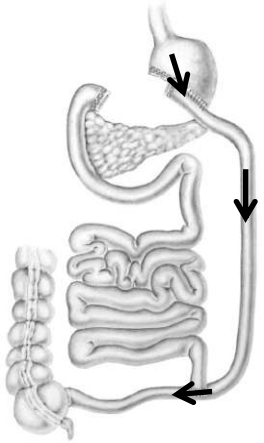
RnY Gastric bypass

Restrictive < mal-absorptive



Mini Gastric bypass

Purely mal-absorptive



BPD (Bilio-pancreatic diversion)

GIP after OGTT	Increased	Reduced	Reduced
GLP-1 after OGTT	Increased	Increased	Increased

Mingrone G.
Nutr Metab Cardiovasc Dis. 2008 Oct;18(8):574-9

GIP in RnY GBP

Reports of GIP level after RnY bypass is inconstant.

TABLE 1. Subject characteristics before and after weight loss, by either diet or GBP

	Hypocaloric diet		RnY GBP		
	Before diet	After diet	Before GBP	After GBP	*P* value
Fasting glucagon (ng/liter)	71.6 ± 10.6	58.5 ± 16.0[a]	65.9 ± 15.0	67.0 ± 21.8	0.002
AUC glucagon (ng/liter^{-1}·min^{-1})	58.1 ± 14.5	49.2 ± 12.4[b]	58.4 ± 10.8	77.3 ± 17.5[b]	0.002
Peak glucagon (ng/liter)	84.7 ± 24.2	68.5 ± 19.7[b]	81.1 ± 14.8	96.9 ± 21.5[b]	0.002
Fasting proinsulin (pmol/liter)	34.6 ± 26.1	16.3 ± 9.6[b]	31.8 ± 17.0	19.2 ± 22.5[a]	0.876
Proinsulin/insulin	0.18 ± 0.11	0.16 ± 0.11	0.19 ± 0.07	0.16 ± 0.19[a]	0.082
Fasting total GLP-1 (pmol/liter)	6.18 ± 2.87	6.34 ± 4.36	6.52 ± 4.06	6.69 ± 3.28	0.998
Peak total GLP-1 (pmol/liter)	18.20 ± 16.33	9.80 ± 5.83	17.49 ± 6.02	112.5 ± 54.3[a]	0.001
AUC total GLP-1 (pmol/liter^{-1}·min^{-1})	8.20 ± 7.29	4.94 ± 1.96	7.55 ± 2.80	31.82 ± 8.10[a]	0.000
Fasting active GLP-1 (pmol/liter)	6.04 ± 3.55	4.28 ± 0.90	7.91 ± 3.77	8.45 ± 4.41	0.216
Peak active GLP-1 (pmol/liter)	10.85 ± 9.73	5.27 ± 1.74	11.21 ± 3.94	24.13 ± 19.31	0.038
AUC active GLP-1 (pmol/liter^{-1}·min^{-1})	6.43 ± 3.69	4.25 ± 0.96	7.38 ± 2.98	10.88 ± 4.94	0.029
Fasting GIP (ng/liter)	34.18 ± 11.41	33.84 ± 33.11	39.27 ± 15.05	40.54 ± 29.87	0.901
Peak GIP (ng/liter)	175 ± 60	208 ± 115	204 ± 56	316 ± 124[a]	0.090
AUC GIP (ng/liter^{-1}·min^{-1})	40.96 ± 12.71	54.00 ± 31.85	48.67 ± 11.35	51.56 ± 18.54	0.399
HOMA-IR	7.96 ± 4.17	4.04 ± 1.91[a]	8.11 ± 3.61	5.16 ± 2.88[b]	0.476

Data are expressed as mean ± SD. Fasting, peak, 120 min, and AUC (total AUC, 180′) values are obtained during the OGTT. The reported *P* value represents the difference between the changes occurring with either weight loss intervention. HOMA-IR, homeostasis model of assessment of insulin resistance.

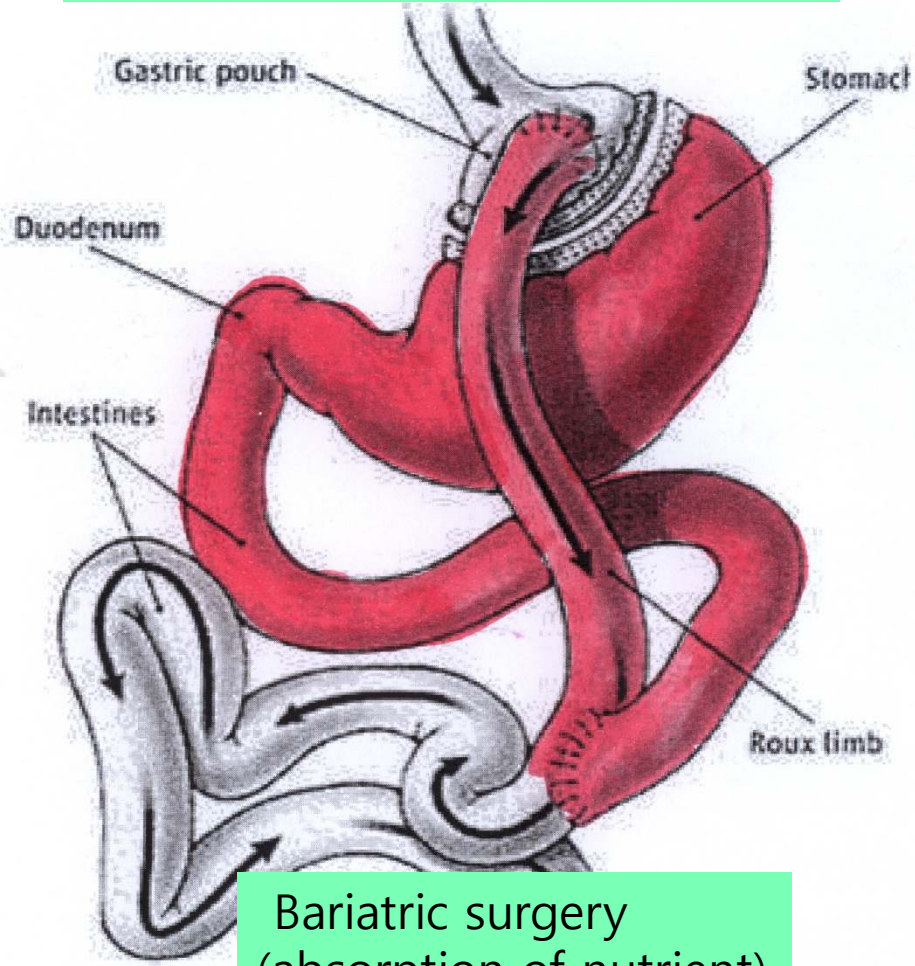
Glucagon and GIP secretions are enhanced in RYGB subjects after meal

Why GIP increases in RnY GBP?

Laferrère B, Teixeira J, et al. ***Effect of weight loss by gastric bypass surgery versus hypocaloric diet on g lucose and incretin levels in patients with type 2 di abetes.*** Clin Endocrinol Metab. 2008 Jul;93(7):2479-85

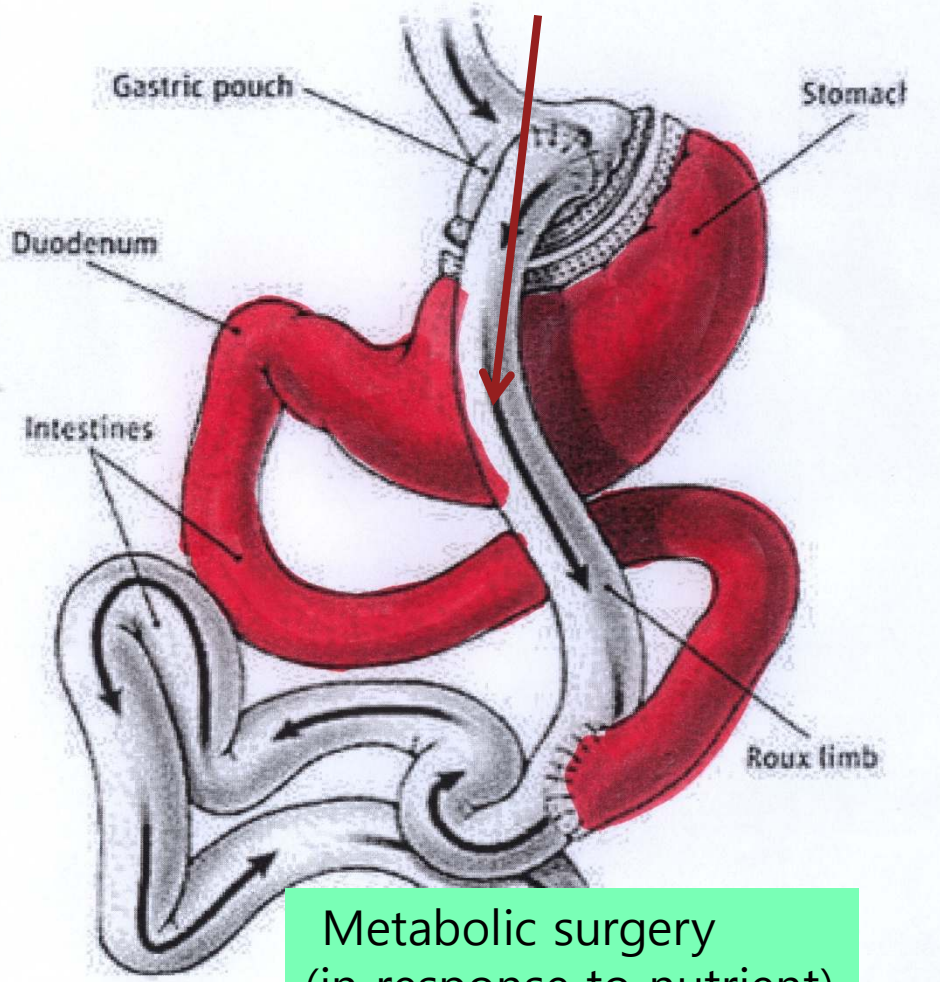
GIP in RnY GBP

Location of defunctionalized limb



Bariatric surgery
(absorption of nutrient)

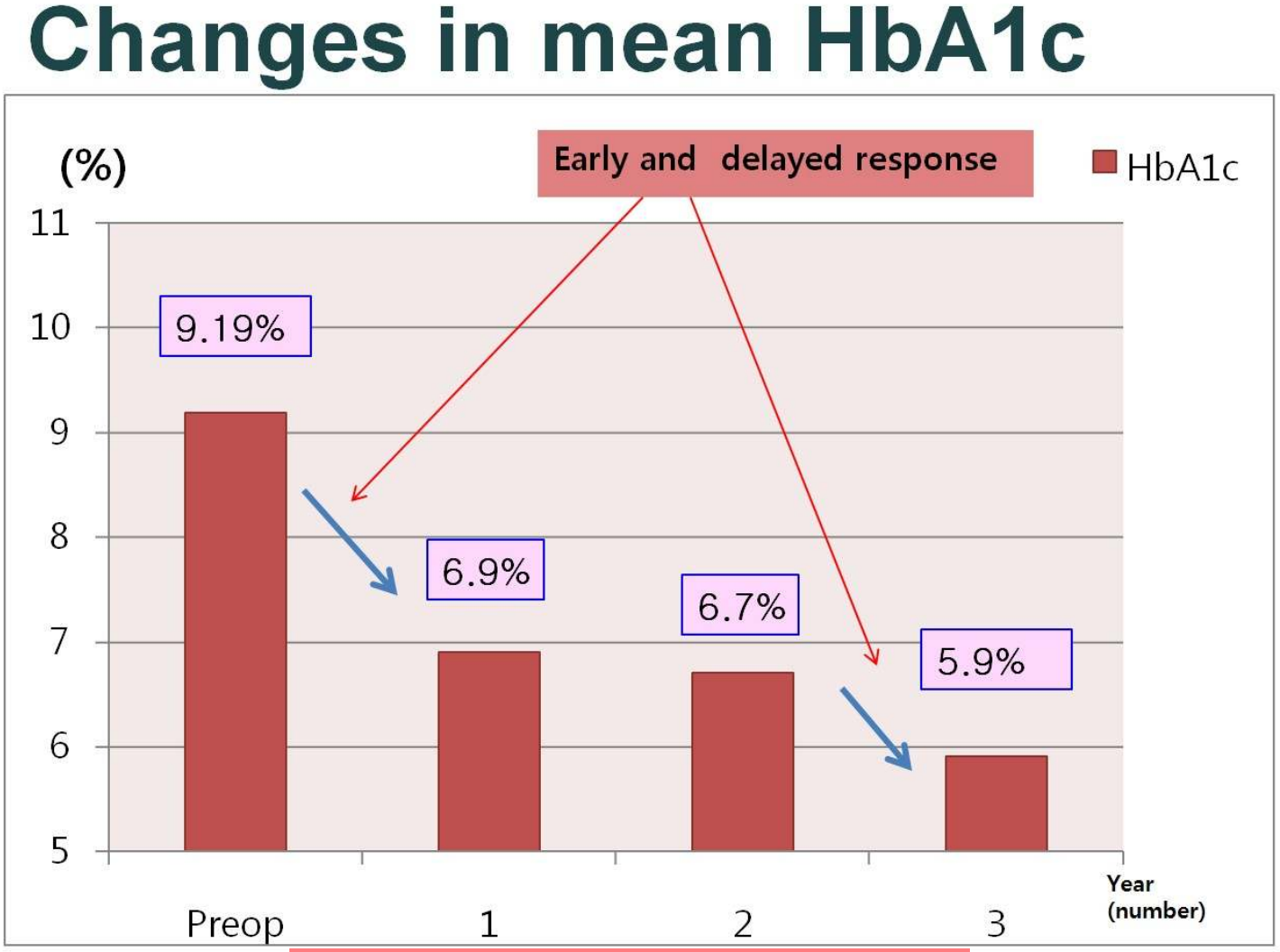
Early exposure of nutrient
To Roux-limb- K cell stimulation



Metabolic surgery
(in response to nutrient)

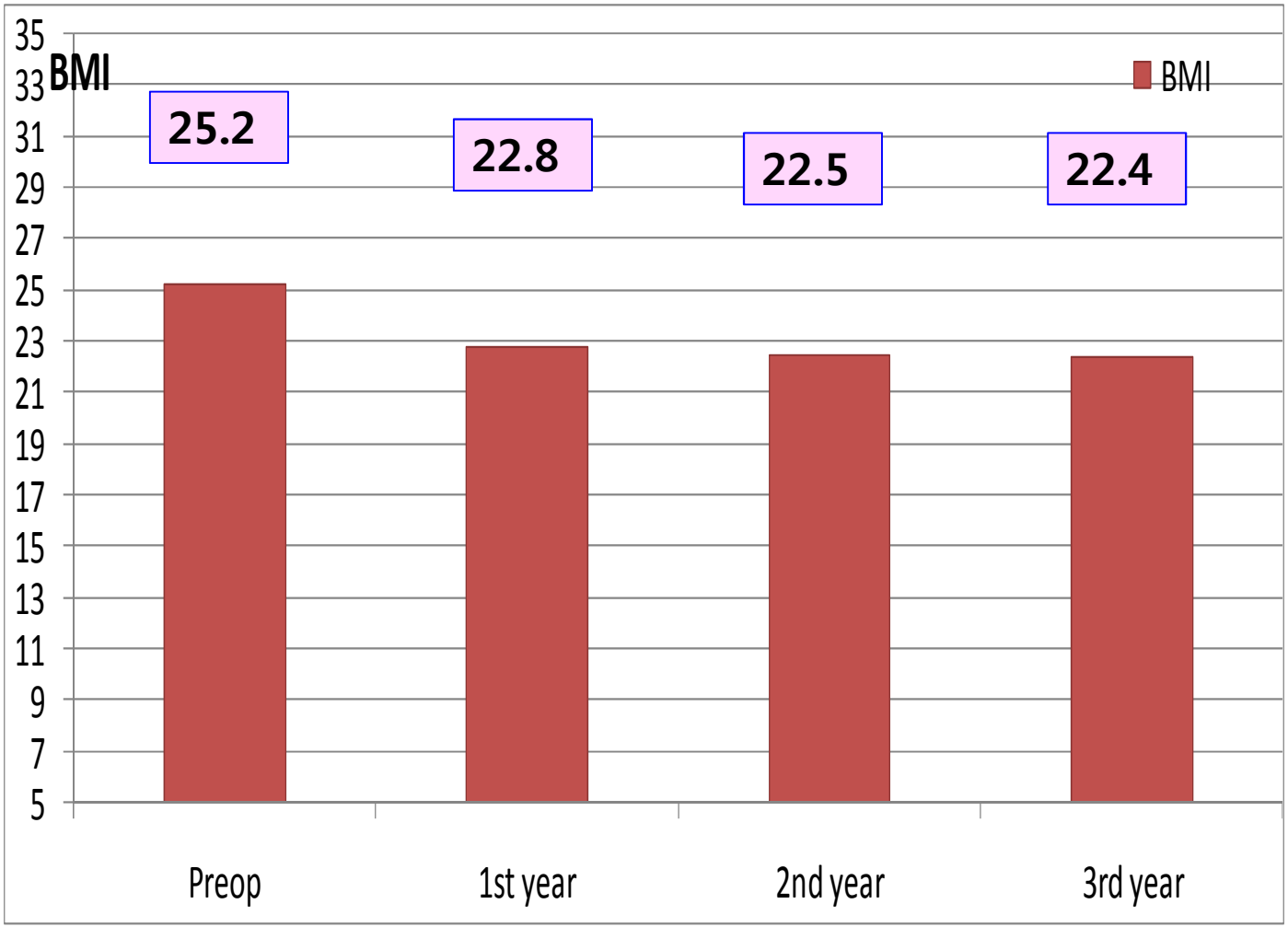
Depends on the length of biliopancreatic limb
The length is different surgeon to surgoen.

Our experience



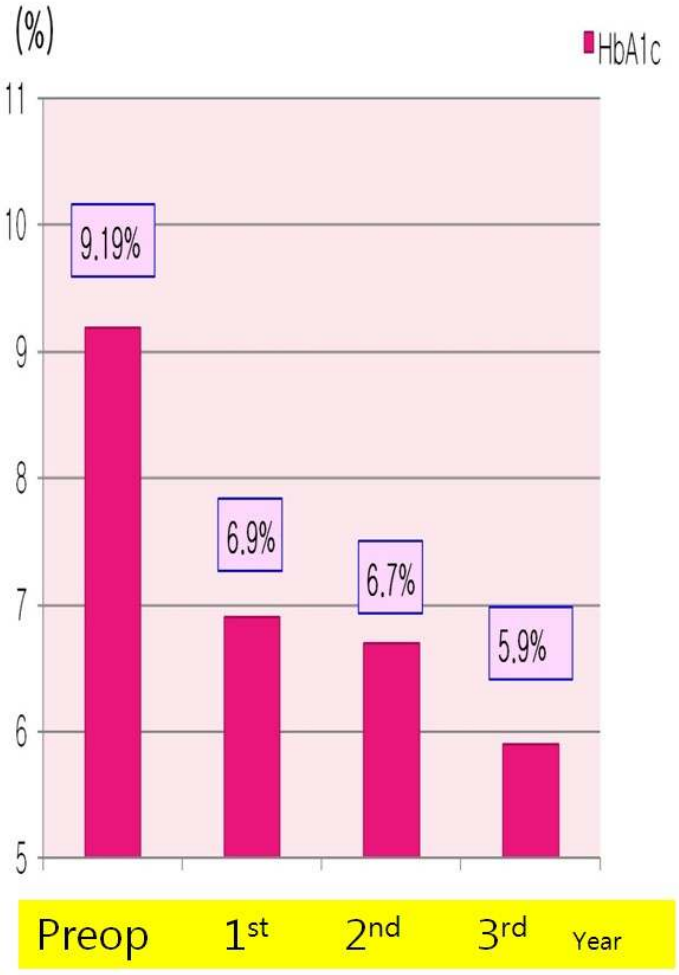
Stagnation between 1st~2nd year

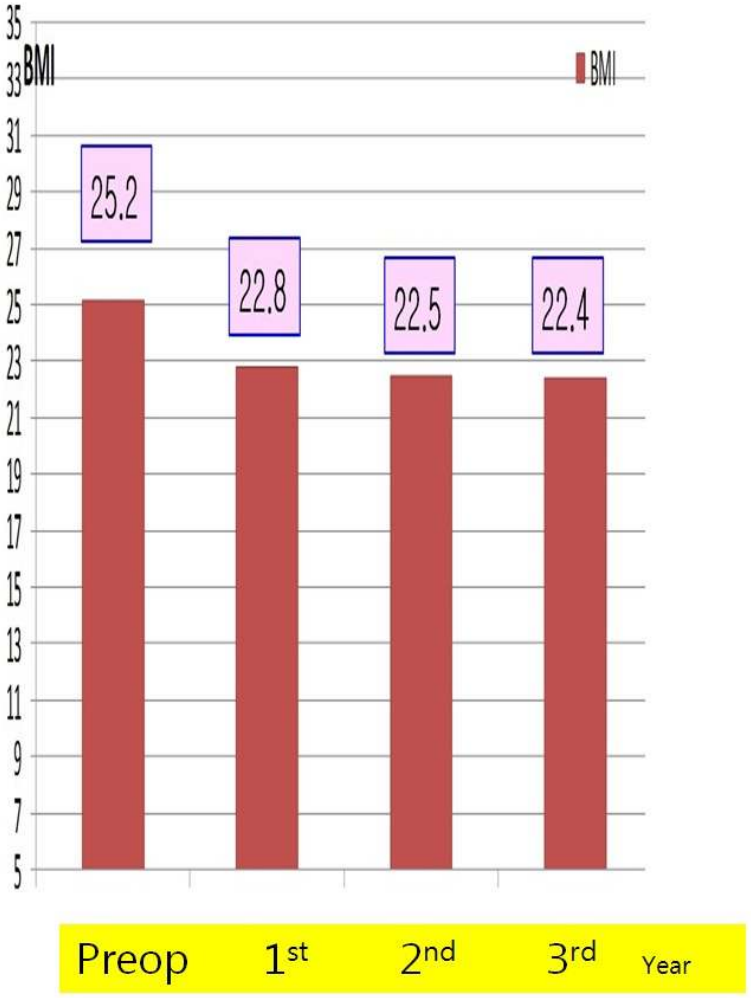
Changes of mean BMI



Our experience

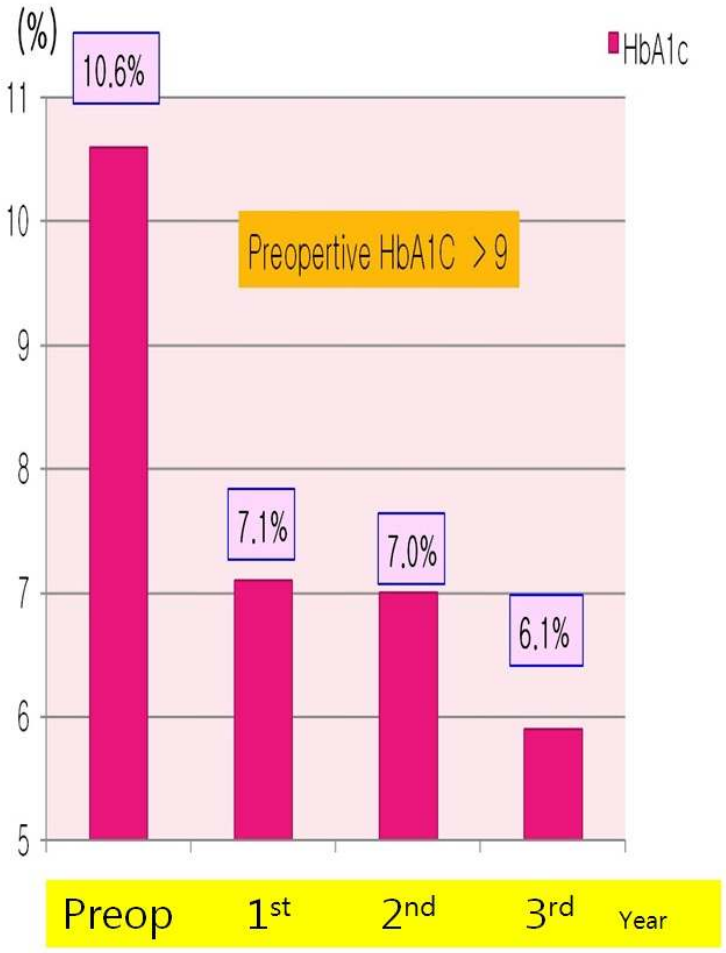
HbA1c vs BMI (independent?)



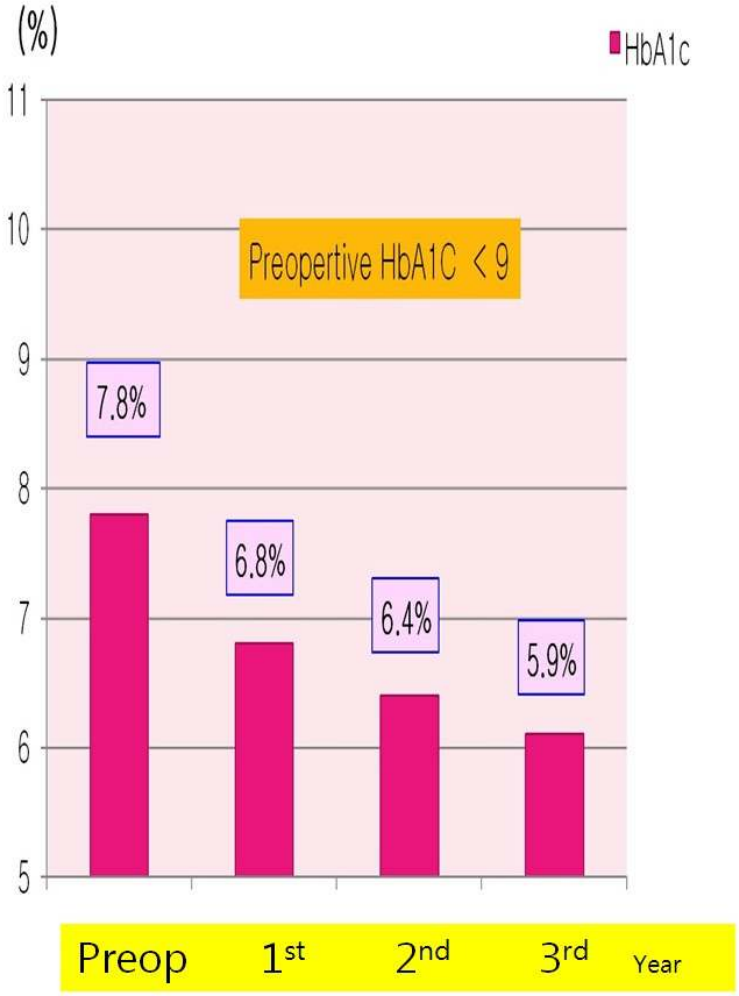


Our experience

High preop. HbA1c group



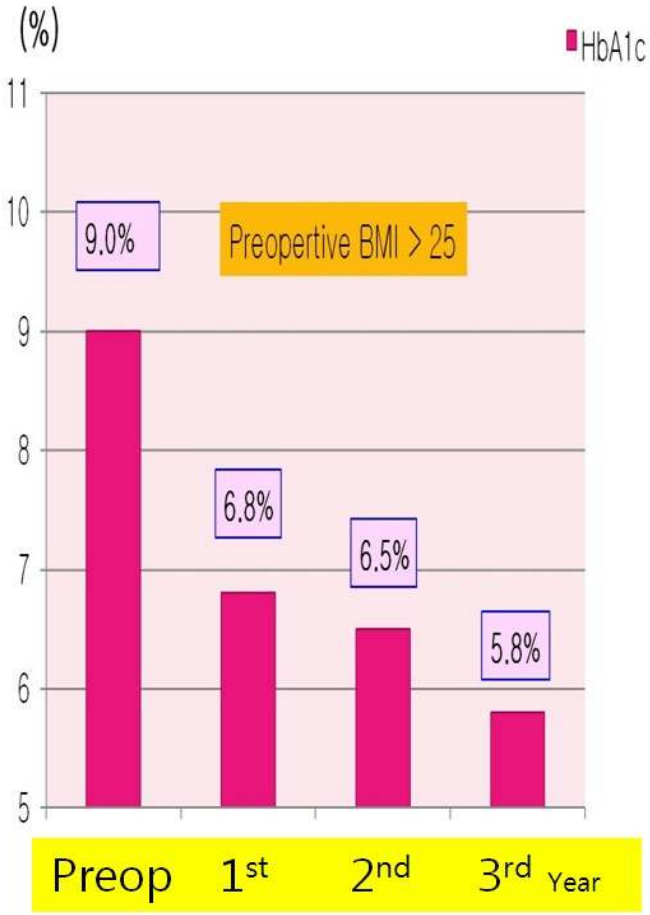
Low preop. HbA1c group



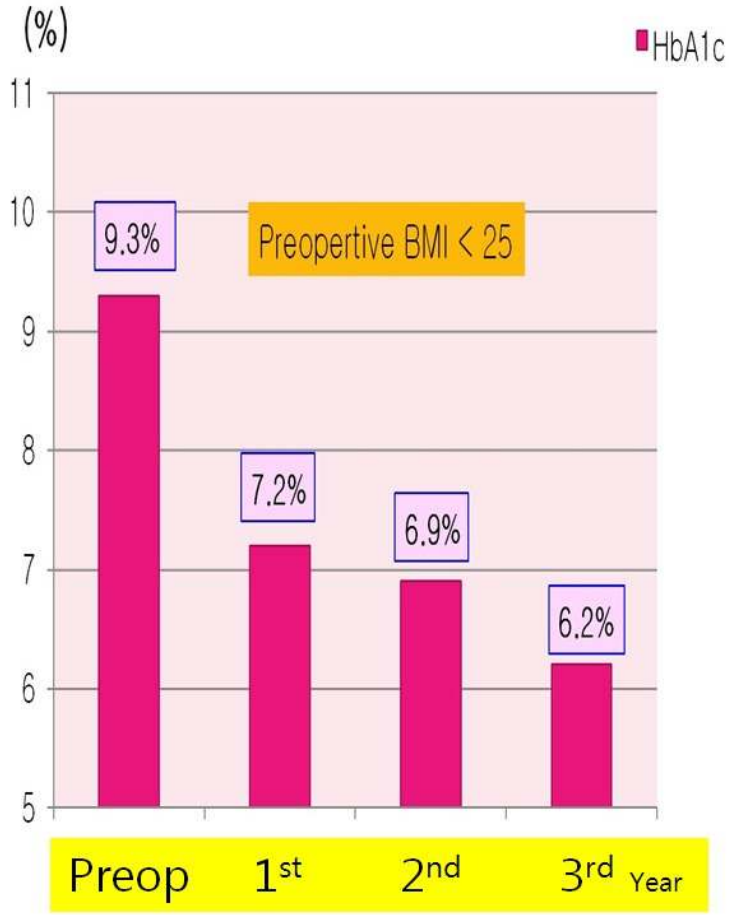
Preopertive HbA1C 9>

Preopertive HbA1C 9 <

Our experience



Preopertive BMI 25>



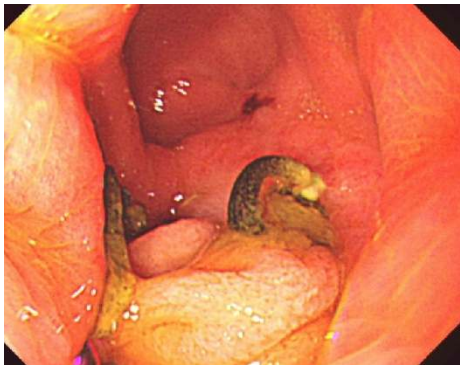
Preopertive BMI 25<

Our experience

Late complication(mostly early period of experience)

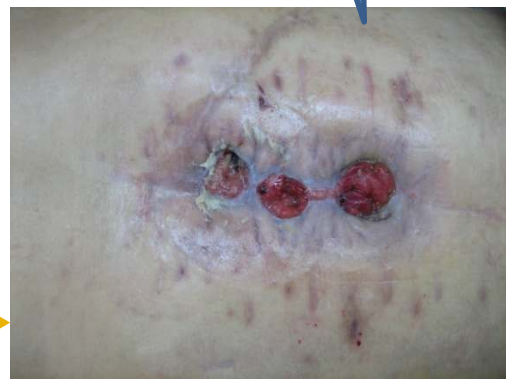
Complication	Number
Anastomosis stenosis	1 (convert to RNY)
Marginal ulcer	19
Iron deficiency anemia	12
Marginal ulcer perforation	1
Acrodermatitis enteropathica (Zinc deficiency)	1
Mortality	0
Postoperative hospital stay (day)	4.7 (3-7)

Diathetic, allergic to all suture material

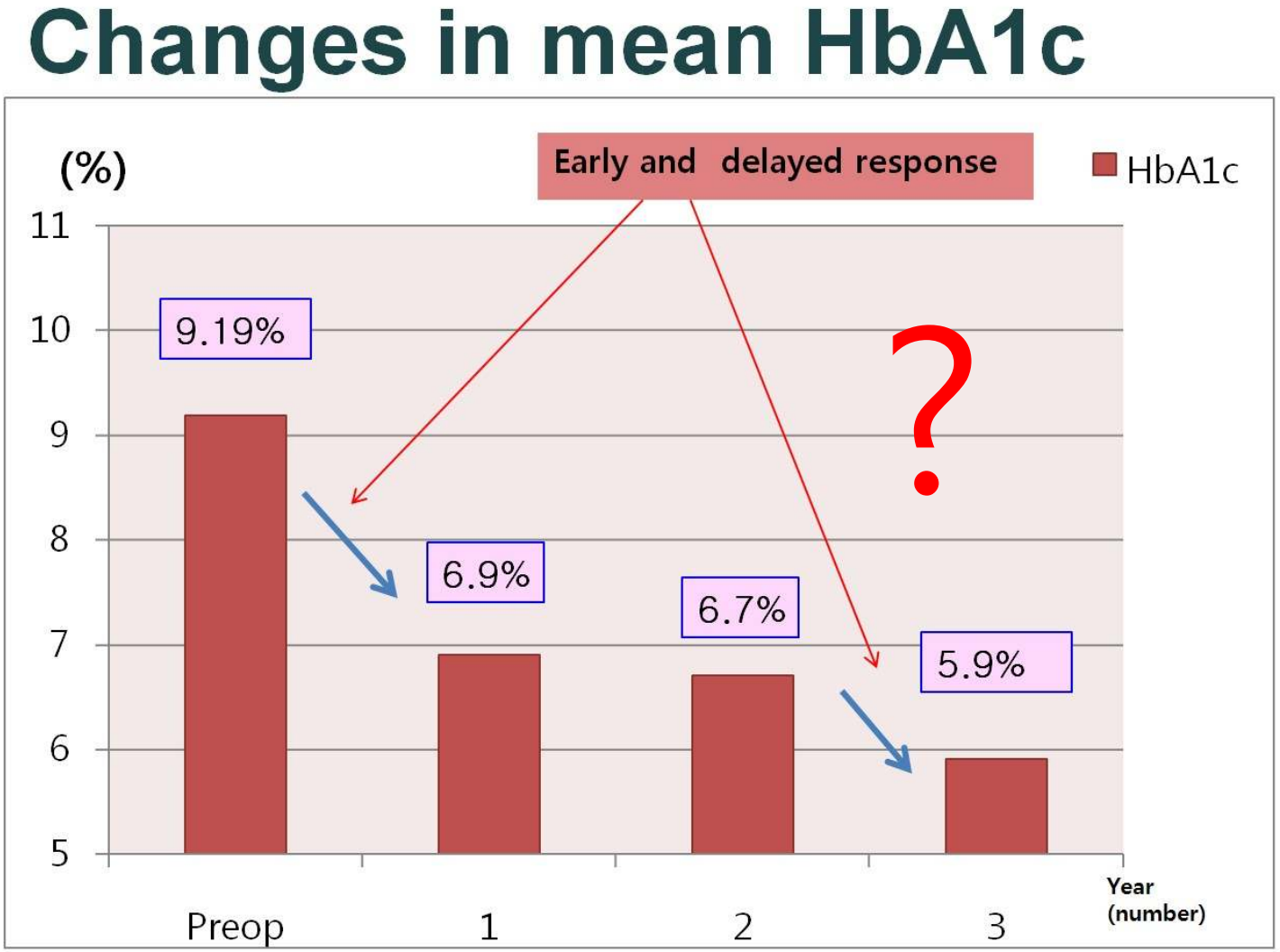


Non absorbable Stitch marginal ulcer

Enterocutaneous fistula



Our experience



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.

Bunck MC, Cornér A, Eliasson B, Heine RJ, Shaginian RM, Taskinen MR, Smith U, Yki-Järvinen H, Diamant M.
Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes.
Diabetes Care. 2011 Sep;34(9):2041-7.

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.

Bunck MC, Cornér A, Eliasson B, Heine RJ, Shaginian RM, Taskinen MR, Smith U, Yki-Järvinen H, Diamant M.
Effects of exenatide on measures of β-cell function after 3 years in metformin-treated patients with type 2 diabetes.
Diabetes Care. 2011 Sep;34(9):2041-7.

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 > or = 3 years exenatide therapy on glycemic control, body weight, cardiometabolic markers, and safety.

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

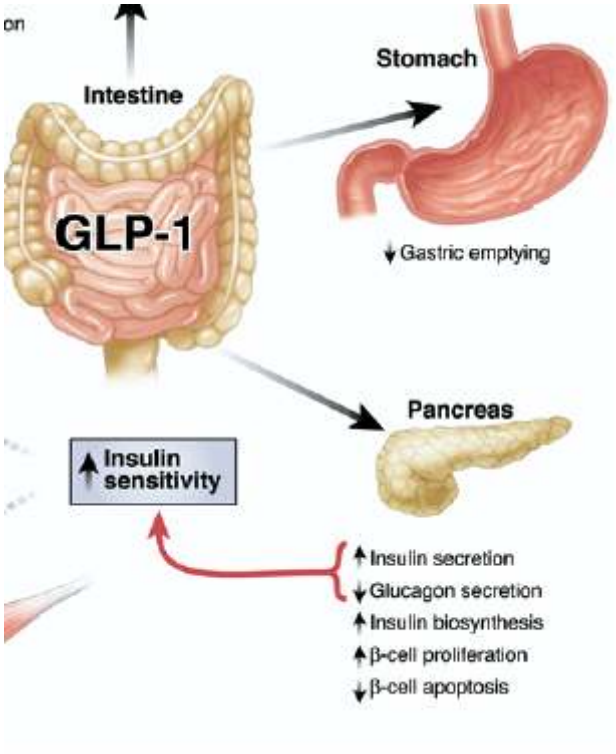
More than 3years treatment of GLP-1 analogue resulted in sustained improvement.

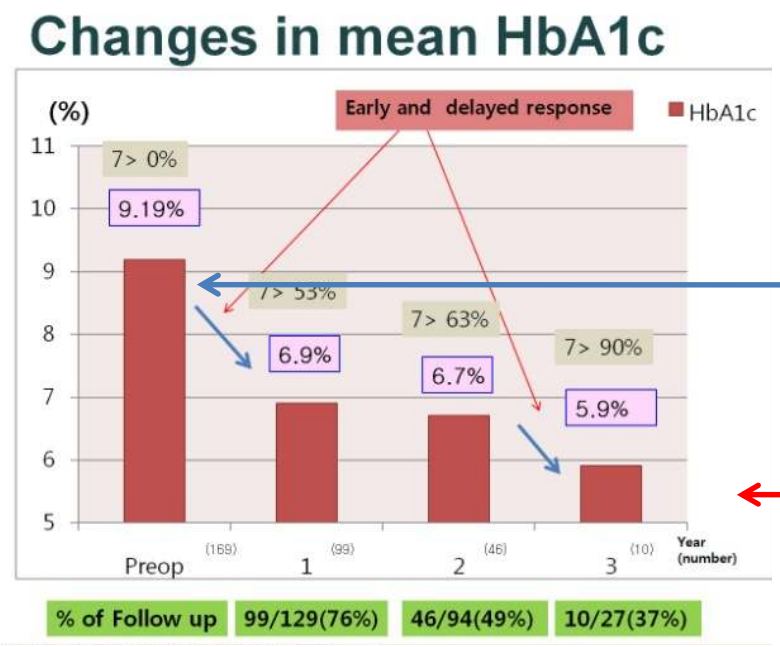
Takes time to promote beta-cell proliferation and islet neogenesis from precusor cells In both in vivo and vitro models of diabetes.

Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, Wintle ME, Maggs DG. ***Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years.*** Curr Med Res Opin. 2008 Jan;24(1):275-86.

Possible causes of early & delayed response

*Biology of **incretins**: GLP-1 and GIP.*
***Baggio** LL, Drucker DJ.*
Gastroenterology. 2007 May;132(6):2131-57. Review.





GIP ↓ GLP-1 ↑

GLP-1 ↑

- ↑ Insulin secretion
- ↓ Glucagon secretion
- ↑ Insulin biosynthesis
- ↑ β-cell proliferation
- ↓ β-cell apoptosis

Additional medication for intractable DM

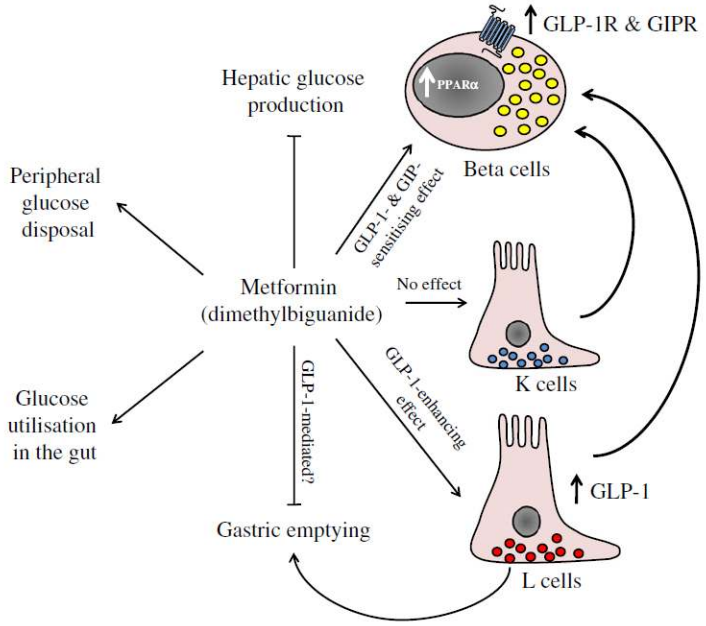
Diabetologia (2011) 54:219–222
DOI 10.1007/s00125-010-1986-3

COMMENTARY

New aspects of an old drug: metformin as a glucagon-like peptide 1 (GLP-1) enhancer and sensitiser

Y. M. Cho · T. J. Kieffer

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

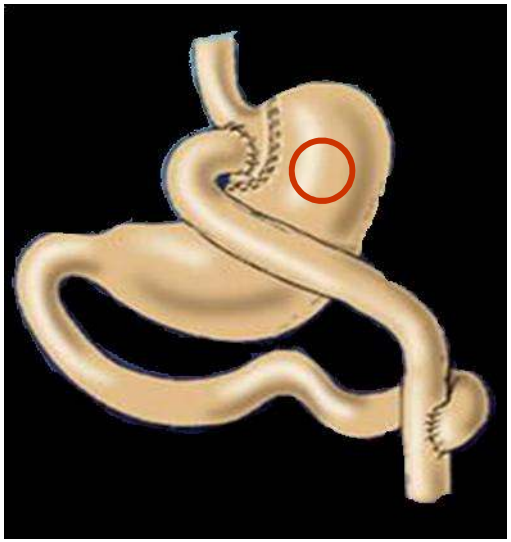


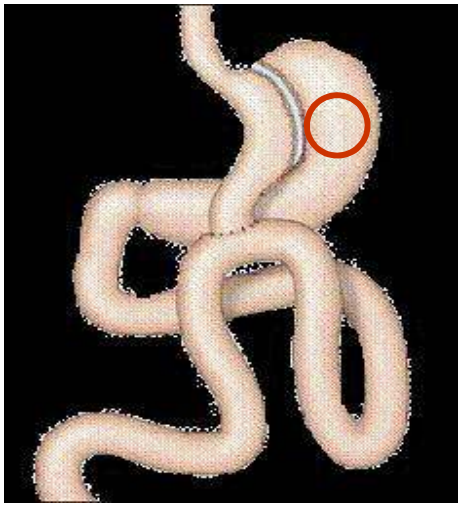
PPAR-α : Peroxisone proliferator-activated receptor alpha

Cho YM, Kieffer TJ. New aspects of an old drug: metformin as a glucagon-like peptide 1 (GLP-1) enhancer and sensitiser. Diabetologia. 2011 Feb;54(2):219-22.

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 caner treatment

Gastric Cancer after Roux-en-Y Gastric Bypass

Alex Escalona, MD[1]; Sergio Guzmán, MD[1]; Luis Ibáñez, MD[1]; Luis Meneses, MD[2]; Alvaro Huete, MD[2]; Antonieta Solar, MD[3]

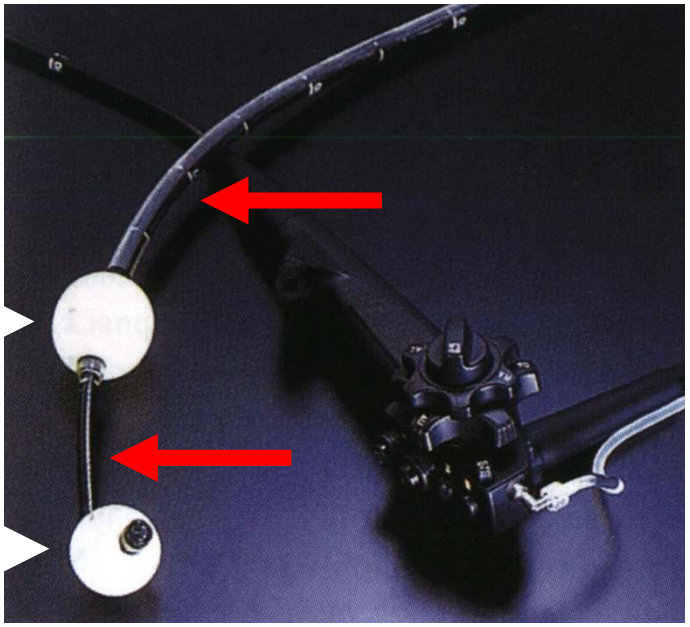
Departments of [1]Digestive Surgery, [2]Radiology and [3]Pathology, Pontificia Universidad Católica de Chile, Santiago, Chile

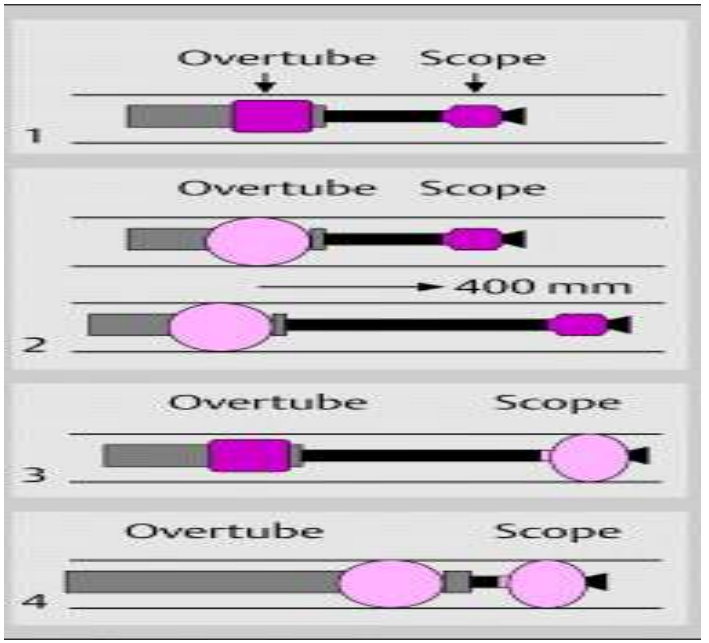
Preoperative evaluation of risk factors for developing cancer may lead to consideration of resection of the excluded stomach at time of RYGBP in selected patients, or the selection of other procedures in which endoscopic surveillance may be performed. Routine gastric resection in patients undergoing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

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

Escalona A et al. Gastric cancer after Roux-en-Y gastric bypass. Obes Surg. 2005 Mar;15(3):423-7.

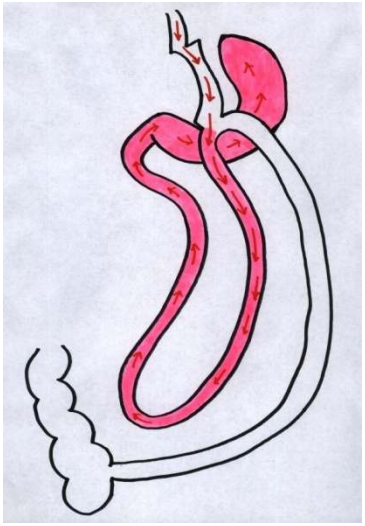
Double balloon enterosocpe

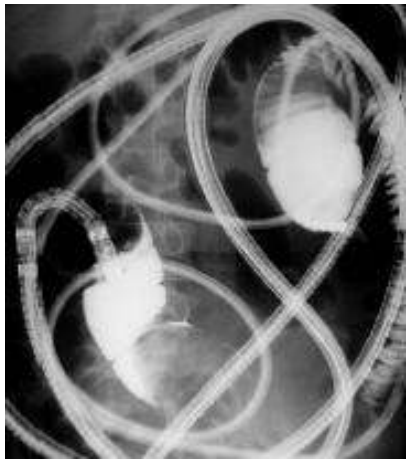


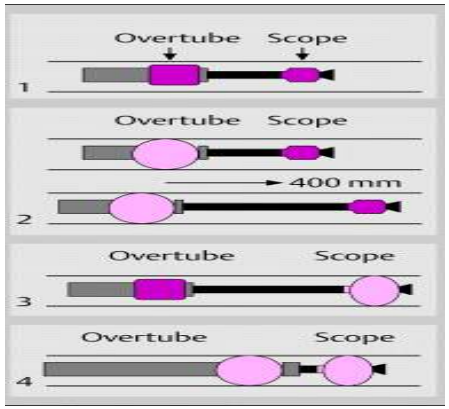


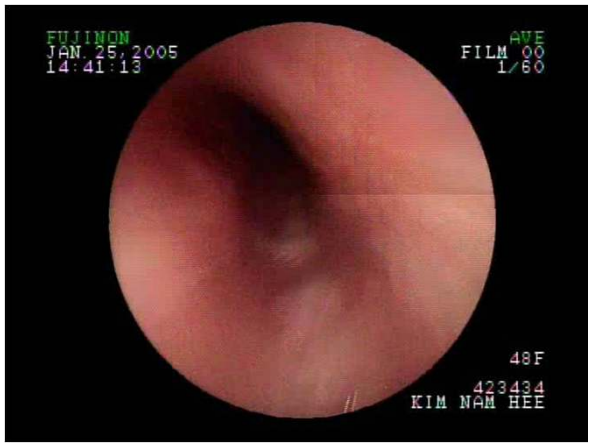
With sequential inflation and deflation of balloon with telescopic movement of two tubes, this scope can reach almost any part of the small intestine freely.

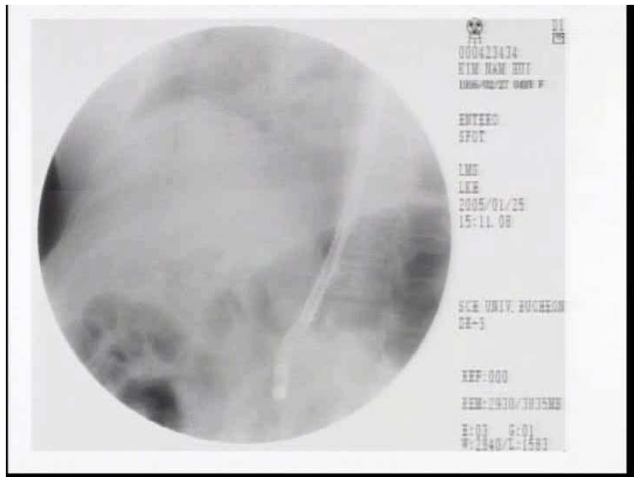
Access to the (bypassed) stomach after gastric bypass-Retrograde gastroduodenoscopy with double balloon enteroscope





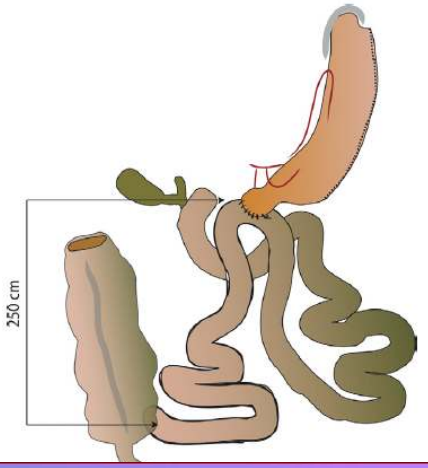




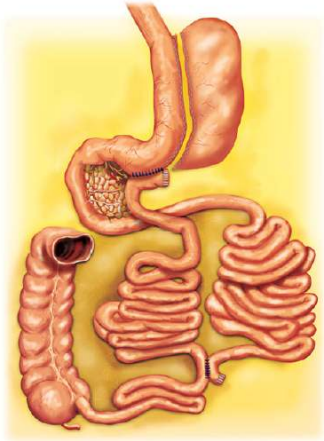


Options for possible gastric cancer in remnant stomach

1. Remove the remnant stomach : resectional gastric bypss



2. Transit bipartition



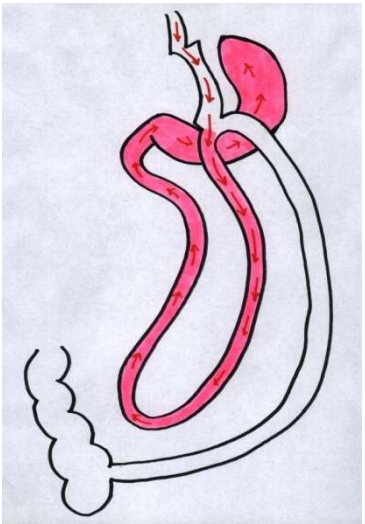
3. Double balloon enteroscope

4. Don't mind

Gastric Cancer after Roux-en-Y Gastric Bypass

Alex Escalona, MD[1]; Sergio Guzmán, MD[1]; Luis Ibáñez, MD[1]; Luis Meneses, MD[2]; Alvaro Huete, MD[2]; Antonieta Solar, MD[3]

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



Routine gastric resection in patients undergoing gastric bypass presents risks which likely outweigh the benefits.

Take home point

STAMPEDE =Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently

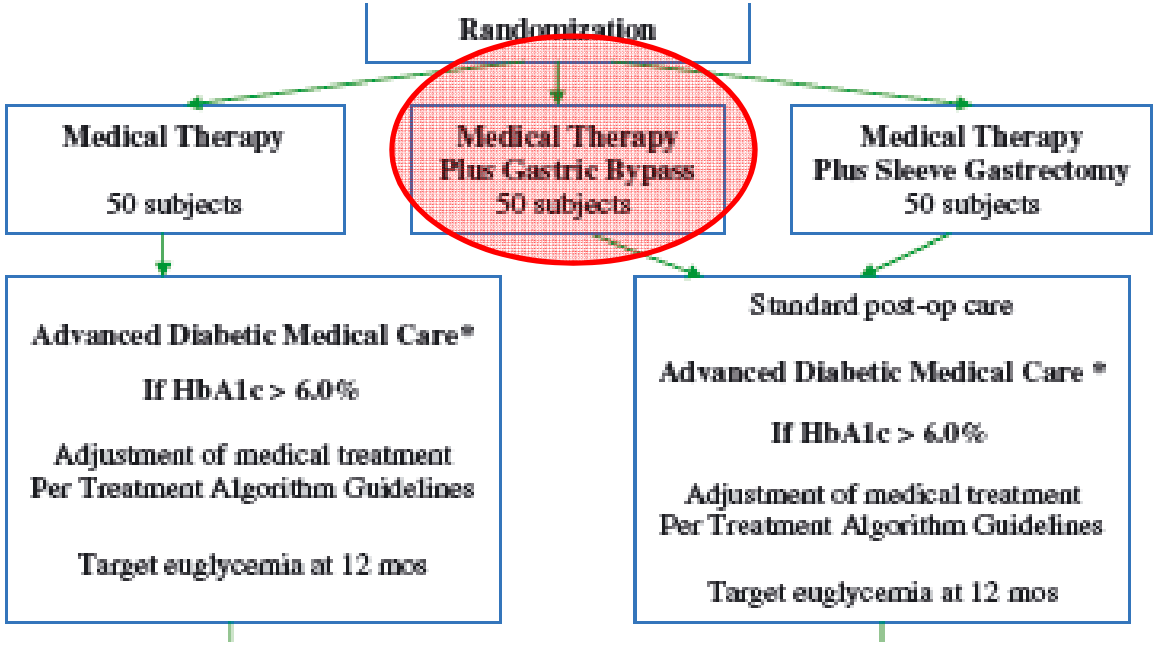
AUGUST 2013 Diabetes Care

In This Issue of *Diabetes Care*

Edited by Helaine E. Resnick, PhD, MPH

Sustained Metabolic Benefits With Bariatric Surgery

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.

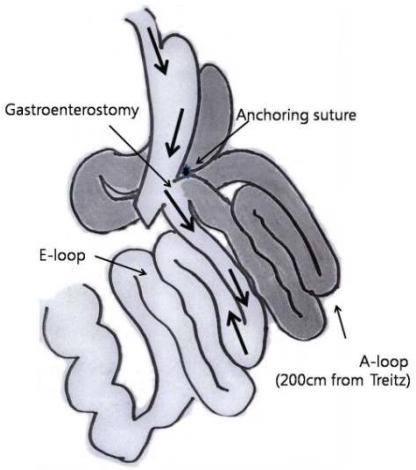


Take home point

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.



▲당뇨병 치료제 종류 및 장단점