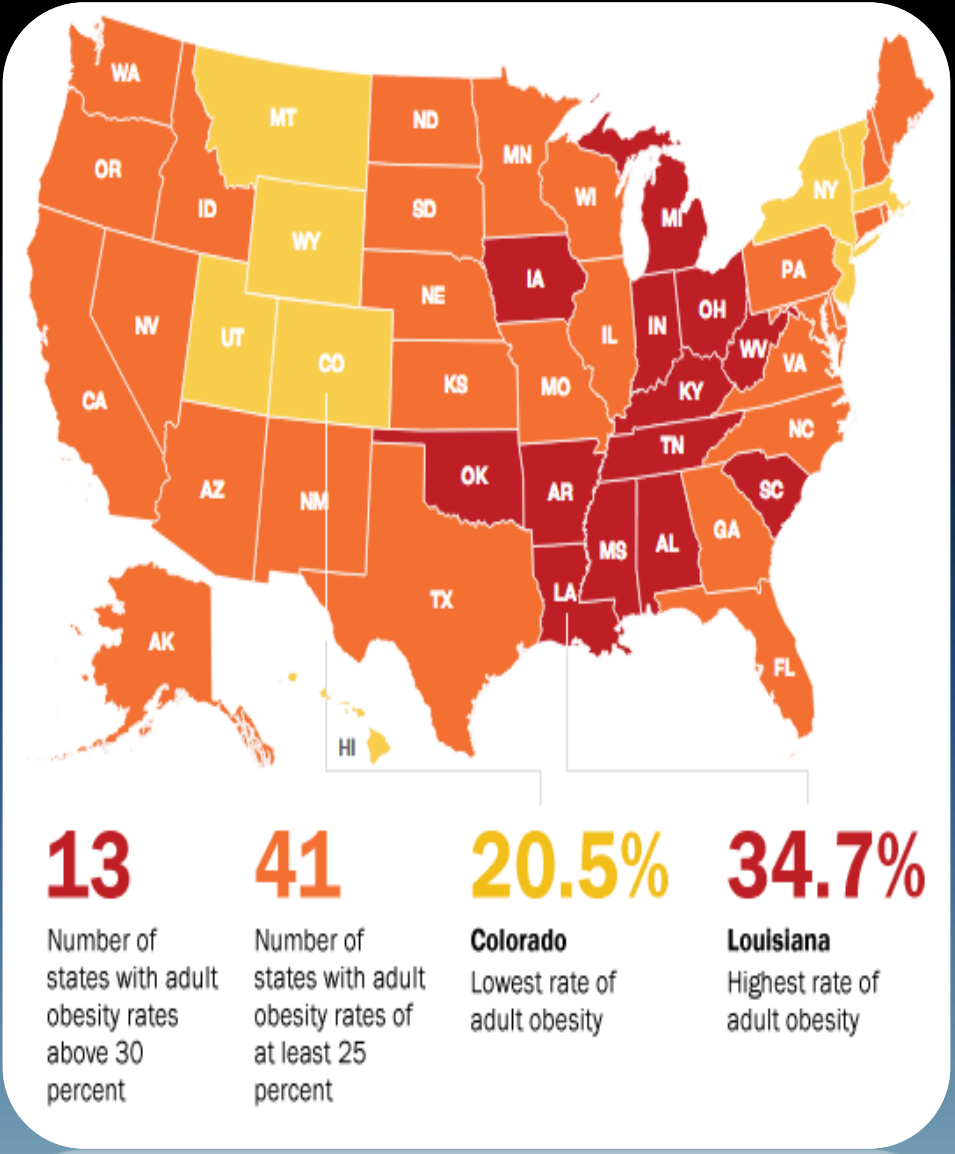
Management of diabetes with Bariatric surgery

Muhammad Jawad MD FACS FASMBS

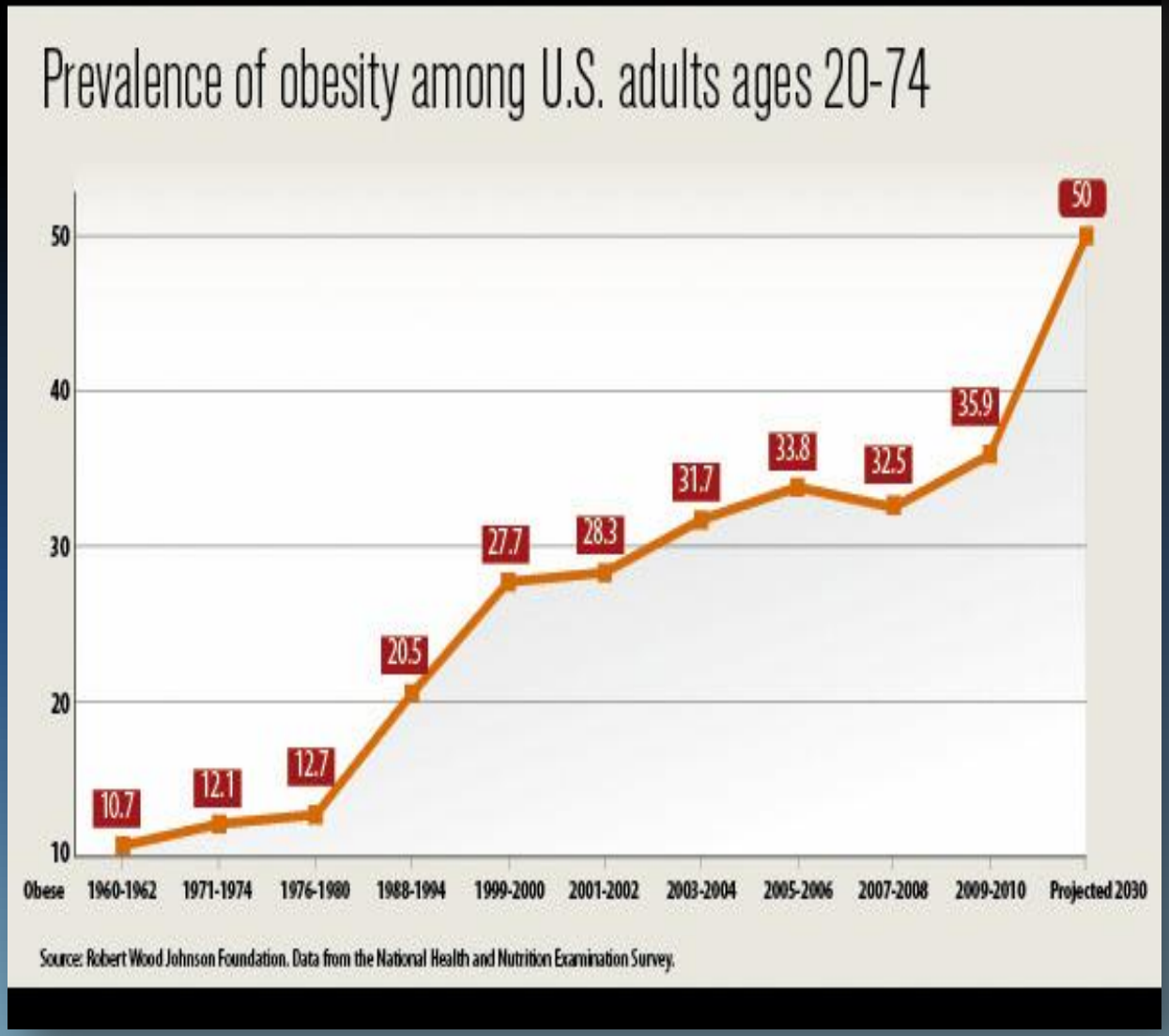
Obesity is common

- Obesity defined as person with BMI 30-35
- Morbid obesity defined as BMI more than 35
- BMI measured ;weight in Kg divided by the height in square meter
- Obesity is global problem with more than 500 million people considered obese in the world
- This problem is affecting the health and the wealth of the world population
- With diabetes ,hypertension ,hyperlipidemia and coronary artery diseases are on the rise

Epidemic of Obesity in USA

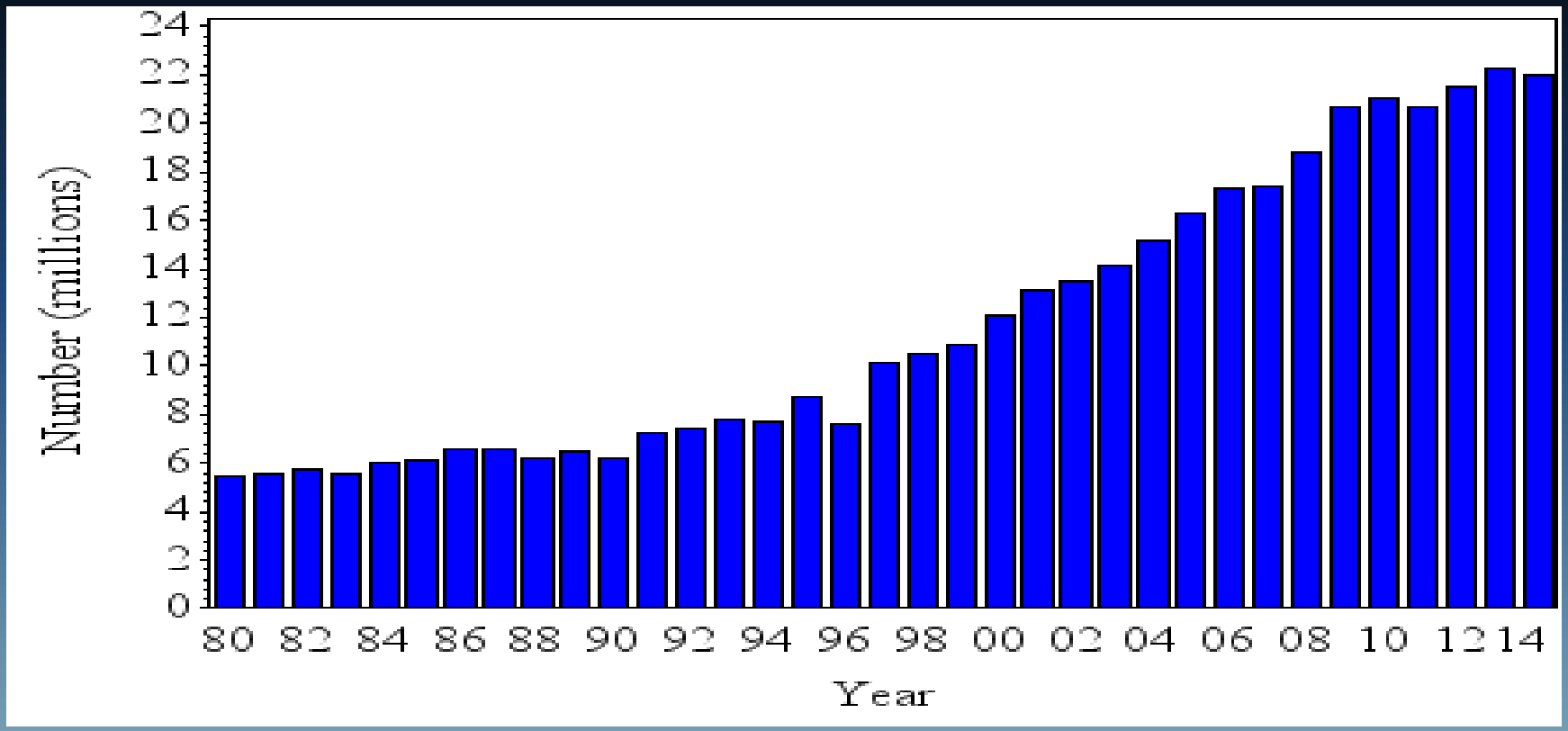


Prevalence of Obesity in USA



Number (in Millions) of Civilian, Non-Institutionalized Persons with Diagnosed Diabetes, United States, 1980-2014

Diabetes is becoming more common in the United States. From 1980 through 2014, the number of Americans with diagnosed diabetes has increased fourfold (from 5.5 million to 22.0 million).



T2DM in USA

- $245 billion annual cost
- 29.1 million or 9.3 % of the US population has DM
- 1.7 million new cases
- Currently 52% of diabetics achieve ADA recommended A1C of 7%
- Pre-diabetic
  - Age > 20 y/o 37%
  - Age > 65 y/o 51%

Obesity promote diabetes

- Increase insulin resistant
- Increase inflammation
- It increase circulating fatty acids
- Increase in adipocyte derived cytokines

Effect of bariatric surgery on type 2 diabetes

- Obesity is potent risk for the development and progression of type 2 diabetes
- Weight loss is the key component in the management and cure of type 2 diabetes
- Diets and life style changes has very poor results in achieving significant and permanent weight loss

Bariatric surgery effect on D.M

- Since the beginning of bariatric surgery in 1953 with J-I bypass, resolution of diabetes was observed even before the weight loss.
- This was observed with all the procedures that was adopted after that.

Bariatric surgery effect

- Enforced caloric restriction
- Enhance insulin sensitivity
- Increase insulin secretion
- After mal absorptive procedure (gastric bypass & biliary pancreatic diversion)normoglycemia is restored within days of the procedure
- After restrictive procedure normoglycemia occur after significant weigh loss

Clinical evidence showed bariatric surgery will result in

- Greater improvement in glycemic control
- Reduction of medication usage
- Reduction in CVD risk
- Reduction of heart attack, stroke , cancer and overall mortality
- Greater weight loss
- Better quality of life

How does bariatric surgery improve type 2 diabetes

- Weight loss decrease insulin resistance and increase sensitivity allowing the Beta cells to rest
- Less lipotoxicity,reduce inflammation by reducing cytokines hormones that secreted by fat cells
- Effect on gut hormones by excluding the duodenum in R-Y gastric bypass and biliary pancreatic diversion
- Effect of bile circulation changes
- Effect on the changes of the microbiata

Obesity Surgery
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Efficacy of the Roux-en-Y Gastric Bypass Compared to Medically Managed Controls in Meeting the American Diabetes Association Composite End Point Goals for Management of Type 2 Diabetes Mellitus

Authors
Authors and affiliations
Daniel B. LeslieEmail author
Robert B. Dorman
Federico J. Serrot
Therese W. Swan
Todd A. Kellogg
Gonzalo Torres-Villalobos
Henry Buchwald
Bridget M. Slusarek
Barbara K. Sampson
John P. Bantle
Sayeed Ikramuddin

The treatment goals recommended by the American Diabetes Association (ADA) for patients with type 2 diabetes mellitus include hemoglobin A1c (HbA1C) <7.0%, low-density lipoprotein (LDL) <100 mg/dL, and systolic blood pressure (SBP) <130 mmHg. Only 10% of conventionally treated patients reach these goals as a composite endpoint

Results

Ultimately, 152 RYGB patients were compared to 115 routine medical management (RMM) patients for whom data on the composite endpoint were available over 2 years. The results show significant decrease in body mass index (kilograms per square meter) in the RYGB group compared to the RMM group ($P < 0.001$). HbA1C, LDL cholesterol, and SBP all significantly improved in the RYGB group (all $P \leq 0.01$) and did not demonstrate any significant change in the RMM group. Over 2 years, when evaluating all three endpoints, the RYGB group (10.5% to 38.2%, $P < 0.001$) demonstrated increased achievement of the ADA goals compared to the RMM group (13.9% to 17.4%, $P = 0.47$). There was a significant decrease in medication use in the RYGB cohort; however, discontinuation of medications was sometimes inappropriate.

The NEW ENGLAND JOURNAL of MEDICINE

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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.

Characteristics of the Patients at Baseline.

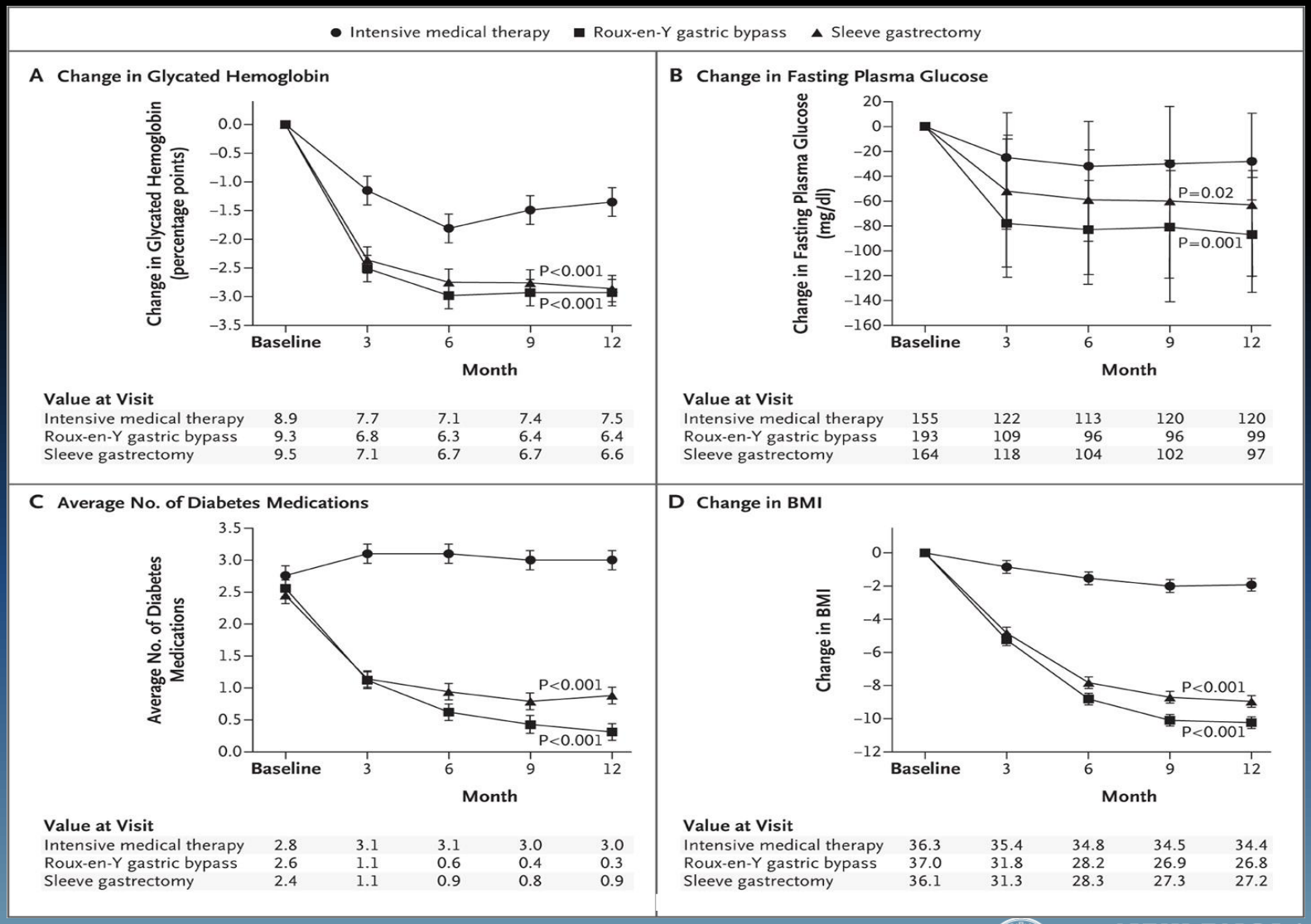
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Medical Therapy (N=50)	Gastric Bypass (N=50)	Sleeve Gastrectomy (N=50)	P Value
Duration of diabetes — yr	8.9±5.8	8.2±5.5	8.5±4.8	0.72
Use of insulin — no. (%)	22 (44)	22 (44)	22 (44)	1.00
Age — yr	49.7±7.4	48.3±8.4	47.9±8.0	0.46
Female sex — no. (%)	31 (62)	29 (58)	39 (78)	0.08
Body-mass index†				
Value	36.8±3.0	37.0±3.3	36.2±3.9	0.42
<35 — no. (%)	19 (38)	14 (28)	18 (36)	0.54
Body weight — kg	106.5±14.7	106.7±14.8	100.8±16.4	0.10
Waist circumference — cm	114.5±9.4	116.4±9.2	114.0±10.4	0.43
Waist-to-hip ratio	0.95±0.09	0.96±0.07	0.96±0.09	0.88
White race — no. (%)‡	37 (74)	37 (74)	36 (72)	0.97
Smoker — no./total no. (%)	15/42 (36)	20/50 (40)	11/50 (22)	0.14
Metabolic syndrome — no. (%)	46 (92)	45 (90)	47 (94)	1.00
History of dyslipidemia — no./total no. (%)	36/43 (84)	44/50 (88)	40/50 (80)	0.55
History of hypertension — no./total no. (%)	26/43 (60)	35/50 (70)	30/50 (60)	0.51

* Plus–minus values are means ±SD. P values are for the overall comparisons.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race was self-reported.

Schauer PR et al. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200225

Changes in Measures of Diabetes Control from Baseline.



Value at Visit					
Intensive medical therapy	8.9	7.7	7.1	7.4	7.5
Roux-en-Y gastric bypass	9.3	6.8	6.3	6.4	6.4
Sleeve gastrectomy	9.5	7.1	6.7	6.7	6.6

Value at Visit					
Intensive medical therapy	155	122	113	120	120
Roux-en-Y gastric bypass	193	109	96	96	99
Sleeve gastrectomy	164	118	104	102	97

Value at Visit					
Intensive medical therapy	2.8	3.1	3.1	3.0	3.0
Roux-en-Y gastric bypass	2.6	1.1	0.6	0.4	0.3
Sleeve gastrectomy	2.4	1.1	0.9	0.8	0.9

Value at Visit					
Intensive medical therapy	36.3	35.4	34.8	34.5	34.4
Roux-en-Y gastric bypass	37.0	31.8	28.2	26.9	26.8
Sleeve gastrectomy	36.1	31.3	28.3	27.3	27.2

The NEW ENGLAND JOURNAL of MEDICINE

Primary Endpoints

- After one year……
- Patients achieving HgA1c of 6.0 or less, whether on or off medications
- 12% of intensive medical treatment group
- 37% in sleeve gastrectomy
- 42% in gastric bypass

Schauer PR et al. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200225

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

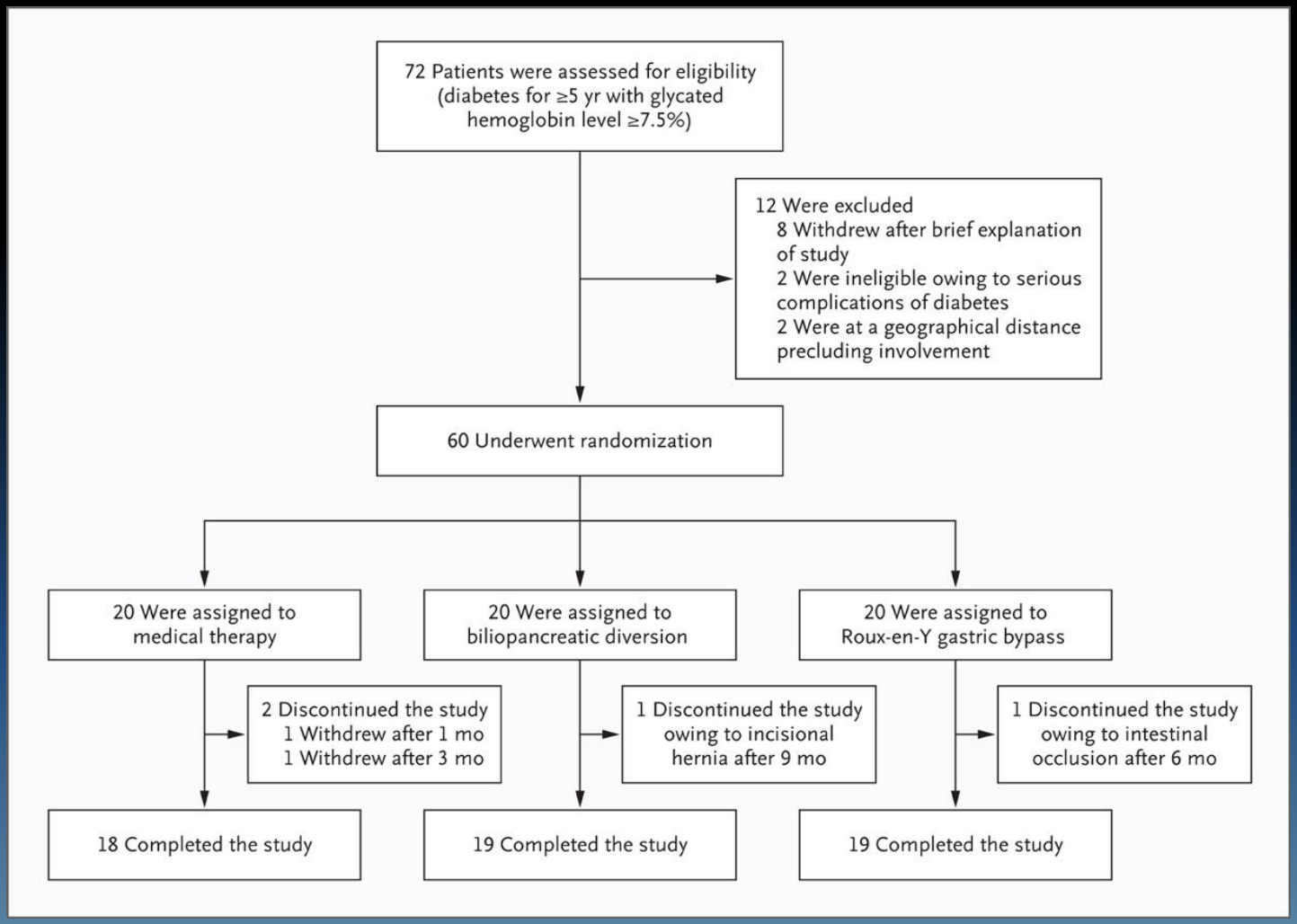
Geltrude Mingrone, M.D., Simona Panunzi, Ph.D., Andrea De Gaetano, M.D., Ph.D., Caterina Guidone, M.D., Amerigo Iaconelli, M.D., Laura Leccesi, M.D., Giuseppe Nanni, M.D., Alfons Pomp, M.D., Marco Castagneto, M.D., Giovanni Ghirlanda, M.D., and Francesco Rubino, M.D.

N Engl J Med 2012; 366:1577-1585April 26, 2012DOI: 10.1056/NEJMoa1200111

this single-center, nonblinded, randomized, controlled trial, 60 patients between the ages of 30 and 60 years with a body-mass index of 35 or more, a history of at least 5 years of diabetes, and a glycated hemoglobin level of 7.0% or more

The primary end point was the rate of diabetes remission at 2 years (defined as a fasting glucose level of <100 mg per deciliter [5.6 mmol per liter] and a glycated hemoglobin level of <6.5% in the absence of pharmacologic therapy).

Enrollment and Outcomes.



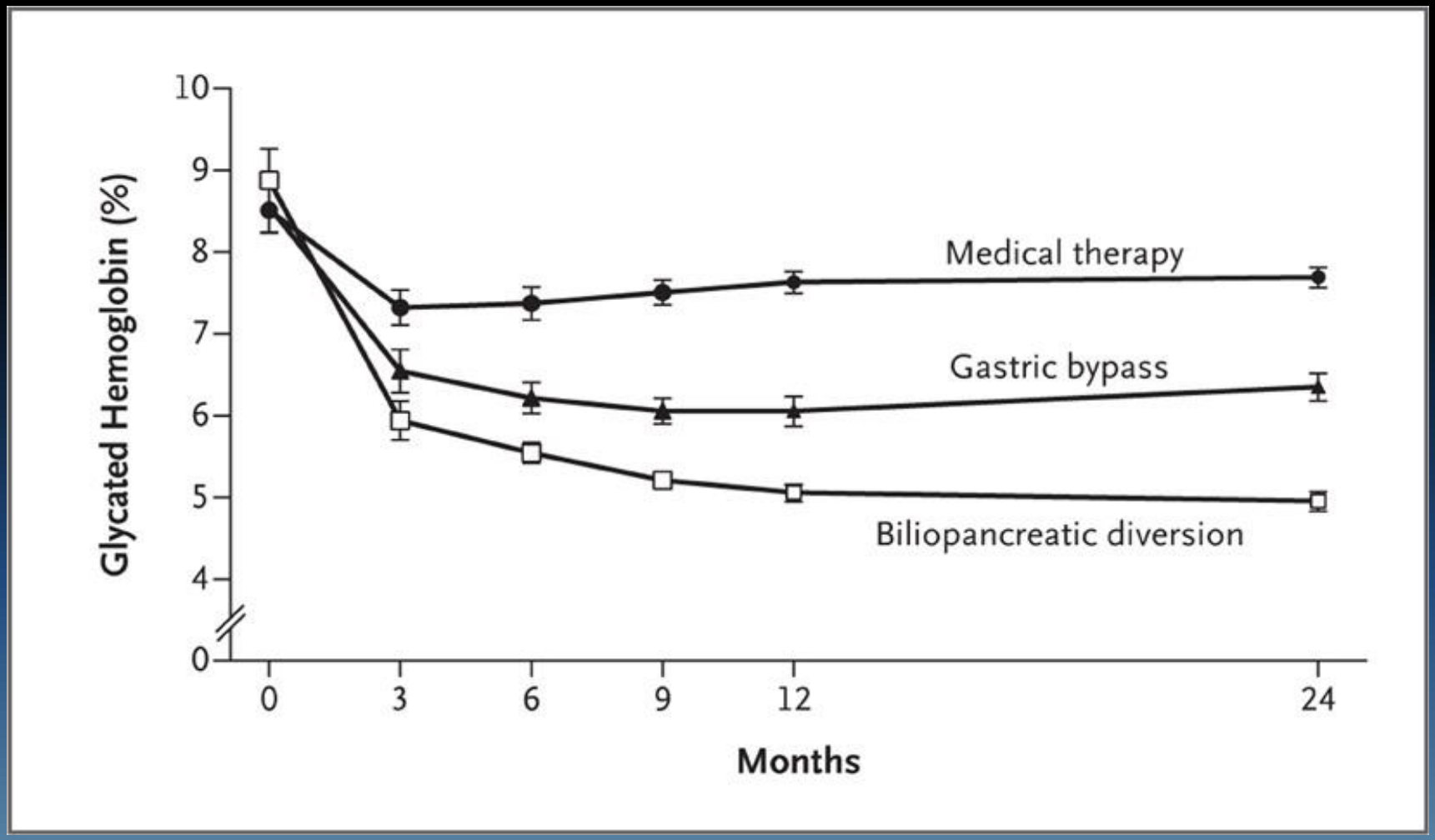
Mingrone G et al. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200111

Results

At 2 years, diabetes remission had occurred in no patients in the medical-therapy group versus 75% in the gastric-bypass group and 95% in the biliopancreatic-diversion group

Age, sex, baseline BMI, duration of diabetes, and weight changes were not significant predictors of diabetes remission at 2 years

Glycated Hemoglobin Levels during 2 Years of Follow-up.



Mingrone G et al. N Engl J Med 2012. DOI: 10.1056/NEJMoa1200111

Interestingly, RYGB differs from BPD in terms of effects on insulin sensitivity and secretion. While BPD results in rapid improvement of insulin sensitivity, with a consequent reduction of insulin secretion [13 , 30] , RYGB improves diabetes control through increased insulin secretion. Indeed, it has been repeatedly shown that RYGB stimulates gastric inhibitory peptide (GIP) and GLP-1 secretion, with stimulation of insulin secretion as a consequence

- Remission of Type 2 Diabetes Mellitus in Patients After Different Types of Bariatric Surgery: A Population-Based Cohort Study in the United Kingdom.
- Yska JP1, van Roon EN2, de Boer A3, Leufkens HG3, Wilffert B4, de Heide LJ5, de Vries F6, Lalmohamed A7.

within the Clinical Practice Research Datalink involving 2978 patients with a record of **bariatric surgery** (2005-2012)

Identifid 569 patients with T2DM

Matched them to 1881 patients with diabetes without **bariatric surgery**.

Results

- 94.5 diabetes mellitus remissions were found in patients who underwent bariatric surgery
- 4.9 diabetes mellitus remissions in matched control patients

- The greatest effect size was observed for gastric bypass (adjusted RR, ; 95% 43.1CI, 19.7-94.5), followed by sleeve gastrectomy (adjusted RR, 16.6; 95% CI, 4.7-58.4) and gastric banding (adjusted RR, 6.9; 95% CI, 3.1-15.2).

Mechanism of diabetic control after bariatric surgery

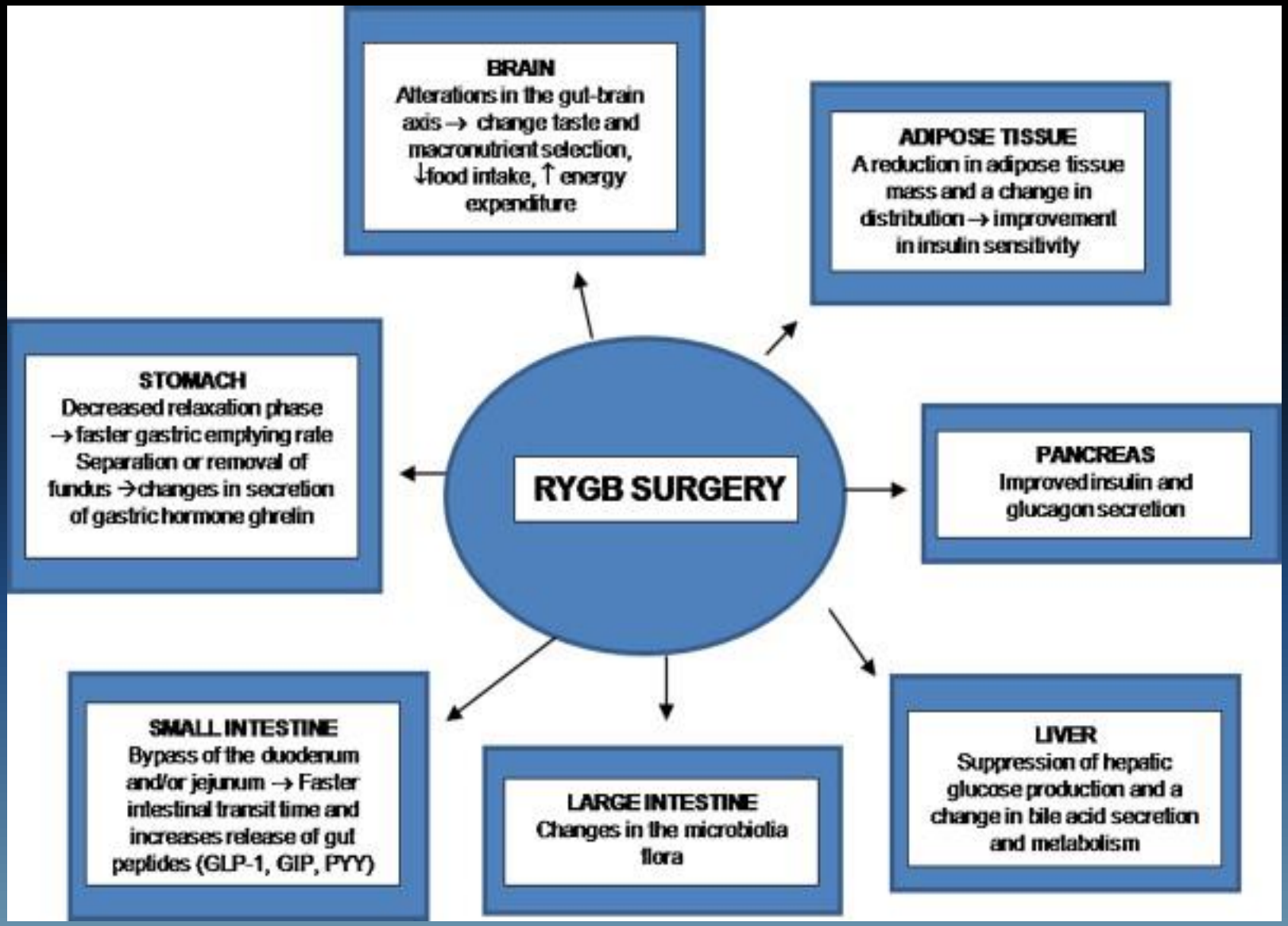
Reduction of caloric intake by portion control

Rapid delivery of the nutrient to distal Intestine will increase the secretions of Incretin gut hormones as in GLP-1 GIP PPY

Exclusion of the proximal intestine and duodenum will suppress the secretion of anti-incretin hormone

Recent studies have shown that improved intestinal gluconeogenesis also involved in glucose homeostasis and improvement of diabetes

. Decrease in fat mass significantly affects circulating levels of adipocytokines, which favorably impact insulin resistance


BRAIN
Alterations in the gut-brain axis → change taste and macronutrient selection, ↓food intake, ↑ energy expenditure
ADIPOSE TISSUE
A reduction in adipose tissue mass and a change in distribution → improvement in insulin sensitivity
STOMACH
Decreased relaxation phase → faster gastric emptying rate
Separation or removal of fundus → changes in secretion of gastric hormone ghrelin
RYGB SURGERY
PANCREAS
Improved insulin and glucagon secretion
SMALL INTESTINE
Bypass of the duodenum and/or jejunum → Faster intestinal transit time and increases release of gut peptides (GLP-1, GIP, PYY)
LARGE INTESTINE
Changes in the microbiotia flora
LIVER
Suppression of hepatic glucose production and a change in bile acid secretion and metabolism

The Mechanism of Diabetes Control After Gastrointestinal Bypass Surgery Reveals a Role of the Proximal Small Intestine in the Pathophysiology of Type 2 Diabetes

Francesco Rubino, MD,* Antonello Forgione, MD,* David E. Cummings, MD,† Michel Vix, MD,* Donatella Gnuli, MD,‡ Geltrude Mingrone, MD,‡ Marco Castagneto, MD,§ and Jacques Marescaux, MD

Goto-Kakizaki (GK) type 2 diabetic rats underwent duodenal-jejunal bypass (DJB), a stomach-preserving RYGB that excludes the proximal intestine

gastrojejunostomy (GJ), which creates a shortcut for ingested nutrients without bypassing any intestine

Controls were pair-fed (PF) sham-operated and untreated GK

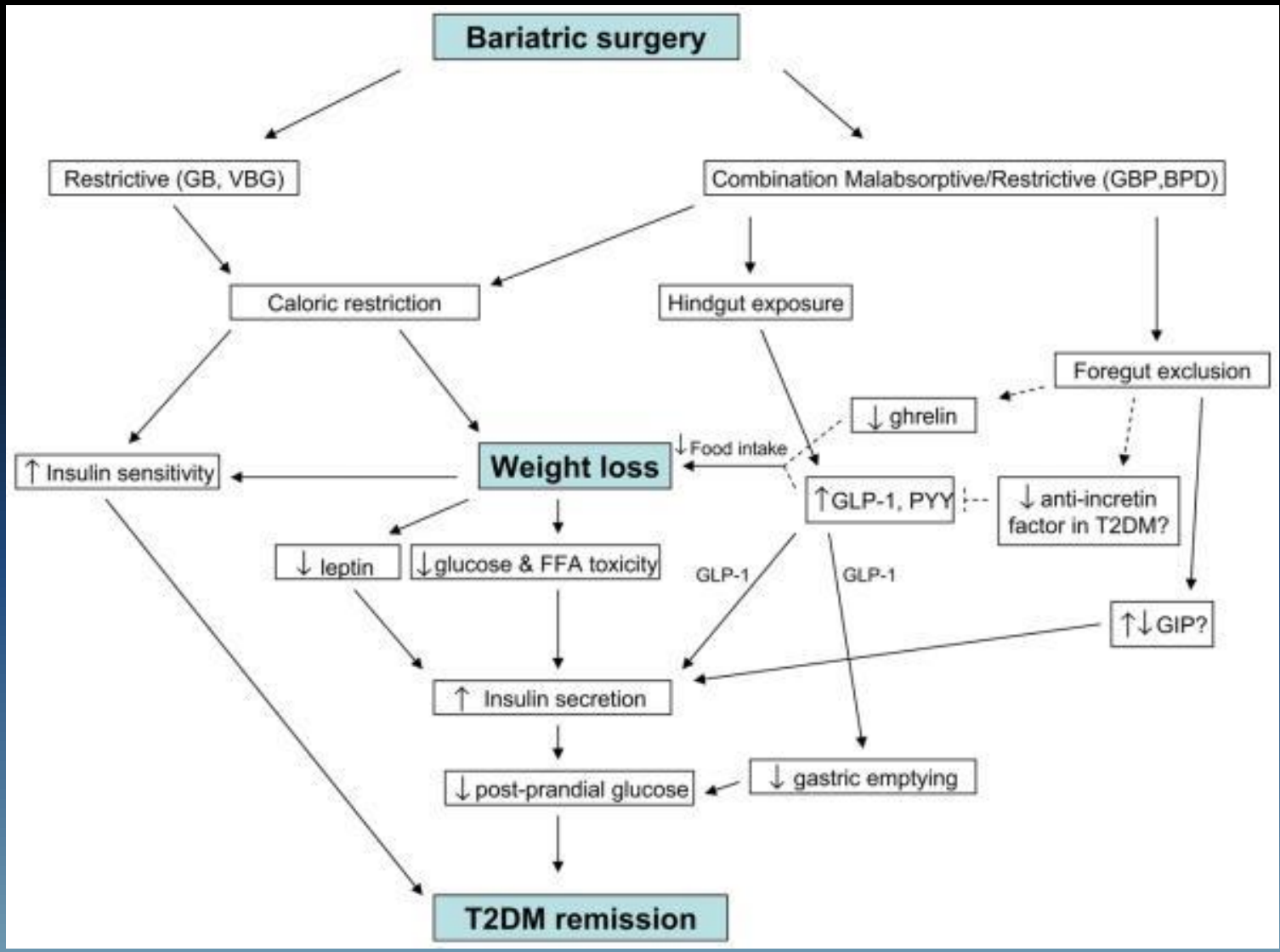
There were no differences in food intake, body weight, or nutrient absorption among surgical groups

DJB-treated rats had markedly better oral glucose tolerance

. GJ did not affect glucose homeostasis, but exclusion of duodenal nutrient passage in re operated GJ rats significantly improved glucose tolerance

Conversely, restoration of duodenal passage in DJB rats reestablished impaired glucose tolerance.

Proposed model for mechanisms of T2DM remission after GBP based on available studies. Dashed lines indicate hypothetical links



GIP is a peptide secreted by the duodenal K-cells in response to ingested fat and carbohydrate

GLP-1 is a peptide secreted by the gut L-cells, and, in type 2 diabetes, its secretion is impaired .

The secretion of GLP-1 influences glucose metabolism by inhibiting glucagon secretion, stimulating insulin secretion, delaying gastric emptying and stimulating glycogenogenesis

Two main hypotheses have been proposed to explain the early effects of metabolic surgery on diabetes: the hindgut hypothesis; and the foregut hypothesis

-Hind gut theory: rapid emptying of the nutrient in the distal bowel will release glucagon like peptide GLP-1 and gastric inhibitory peptide GIP this will stimulate and increase insulin secretion

-The foregut theory:
  Exclusion of the proximal small intestine reduces or suppresses the secretion of anti-incretin hormones

- gastric bypass can also bring about significant improvement in hepatic insulin sensitivity, most likely through reduced hepatic gluconeogenesis and without affecting peripheral insulin sensitivity

. Thus, insulin over secretion together with the quicker absorption of ingested glucose and other carbohydrates could explain the reported post absorptive episodes of hypoglycaemia

Also, sporadic cases of nesidioblastosis have been reported after RYGB for morbid obesity

Nesidioblastosis refers to inappropriate insulin secretion resulting in recurrent severe hypoglycaemia, and is related to hypertrophy and hyperplasia of the islets of Langerhans

Obesity Surgery

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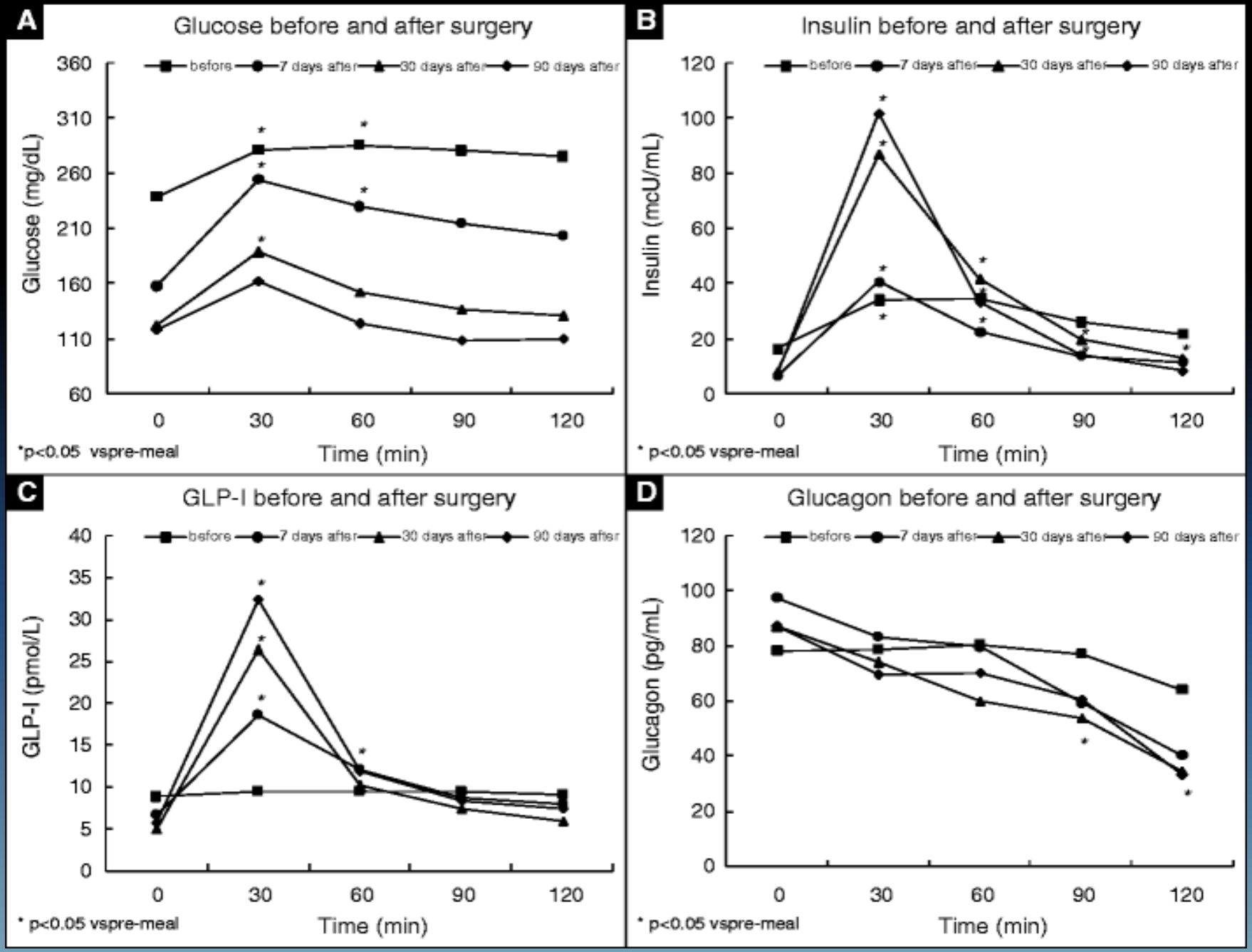
Early Improvement in Glycemic Control After Bariatric Surgery and Its Relationships with Insulin, GLP-1, and Glucagon Secretion in Type 2 Diabetic Patients

Authors

Authors and affiliations

Luciana Mela Umeda Email author ,
Eliana A. Silva,
Glaucia Carneiro,
Carlos H. Arasaki,
Bruno Geloneze,
Maria Teresa Zanella

Ten patients with T2DM (BMI, 39.7 ± 1.9) were evaluated before and 7, 30, and 90 days after RYGB. A meal test was performed, and plasma insulin, glucose, glucagon, and glucagon-like-peptide 1 (GLP-1) levels were measured at fasting and postprandially.


A
Glucose before and after surgery
before
7 days after
30 days after
90 days after
Glucose (mg/dL)
360
310
260
210
160
110
60
0
30
60
90
120
Time (min)
*p<0.05 vspre-meal
B
Insulin before and after surgery
before
7 days after
30 days after
90 days after
Insulin (mcU/mL)
120
100
80
60
40
20
0
0
30
60
90
120
Time (min)
* p<0.05 vspre-meal
C
GLP-I before and after surgery
before
7 days after
30 days after
90 days after
GLP-I (pmol/L)
40
35
30
25
20
15
10
5
0
0
30
60
90
120
Time (min)
* p<0.05 vspre-meal
D
Glucagon before and after surgery
before
7 days after
30 days after
90 days after
Glucagon (pg/mL)
120
100
80
60
40
20
0
0
30
60
90
120
Time (min)
* p<0.05 vspre-meal

Obes Surg. 2009 Sep;19(9):1297-303. doi: 10.1007/s11695-009-9870-2. Epub 2009 Jul 23.

The surgical treatment of type II diabetes mellitus: changes in HOMA Insulin resistance in the first year following laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic adjustable gastric banding (LAGB).

Ballantyne GH1, Wasielewski A, Saunders JK.

Effects of energy restriction on diabetes

. Four days of dieting (reducing energy intake by around 1000 kcal/d) led to a large increase in insulin suppression of hepatic glucose output and, thus, increased hepatic insulin sensitivity
This suggests that energy restriction and weight loss may have independent effects on glucose control

Seven days after RYGB, a significant reduction was observed in HOMA-IR index from 7.8 ± 5.5 to 2.6 ± 1.7; $p < 0.05$ was associated with a nonsignificant reduction in body weight,
reductions in both fasting blood glucose and insulin levels lead to marked reduction in HOMA-IR index

Surgical Endoscopy

June 2010, Volume 24, Issue 6, pp 1367–1373

Reactivation of adiponectin expression in obese patients after bariatric surgery

Authors

Authors and affiliations

A. Katharine Hindle,
Claire Edwards,
Tim McCaffrey,
Sidney W. Fu,
Fred Brody

Effect of weight loss

. Currently, adipose tissue is viewed as an endocrine organ because it secretes a variety of cytokines that affect other organs

The circulating cytokines secreted from adipose tissue modulate insulin sensitivity and resistance

Furthermore, adipocyte-derived free fatty acids contribute to insulin resistance in the liver and in muscle tissue

Adiponectin is one of the cytokines that is secreted by adipose tissue

The data from this study showed a statistically significant downregulation of adiponectin expression in preoperative obese patients compared with the postoperative group

Interestingly, RYGB differs from BPD in terms of effects on insulin sensitivity and secretion. While BPD results in rapid improvement of insulin sensitivity, with a consequent reduction of insulin secretion

RYGB stimulates gastric inhibitory peptide (GIP) and GLP-1 secretion, with stimulation of insulin secretion as a consequence

Thus, insulin over secretion together with the quicker absorption of ingested glucose and other carbohydrates could explain the reported post absorptive episodes of hypoglycaemia.

Nesidioblastosis refers to inappropriate insulin secretion resulting in recurrent severe hypoglycaemia, and is related to hypertrophy and hyperplasia of the islets of Langerhans

Levels of GLP-1, PYY, and ghrelin decrease in obese patients and decrease even further in diabetic patients by mechanisms that are unknown. In contrast, GIP levels may be normal to increased in diabetic patients.

Bariatric procedures that expedite nutrient delivery to the distal ileum, such as BPD and RYGB, increase GLP-1 and PYY levels. In contrast, restrictive procedures do not increase levels of incretins or PYY

Augmented levels of GLP-1 probably account for the antidiabetic effect of procedures that bypass the small bowel

In addition, altered secretion of anorexigenic peptides, such as GLP-1 and PYY, may mediate the reduction in appetite and sustained weight loss that occurs more often after intestinal bypass procedures.

Ghrelin levels after surgery are determined by the remaining amount of residual ghrelin-producing tissue and by whether vagal innervation is intact

Studies in rats showed that bile delivered to the ileum, as opposed to the duodenum in intact rats, led to increased satiety hormone levels

. BA have been shown to inhibit weight and adiposity gain in mice via increased thyroid-hormone mediated energy expenditure in brown adipose tissue and it is possible that this mechanism could be relevant to post-RYGB patients

Evidence from rats and humans shows that gut microflora are different in lean versus obese subjects

individuals with diabetes have reduced proportions of Firmicutes and Clostridia

Studies investigating microbiota in subjects after RYGB found substantial differences in the intestinal environment post-RYGB

Individuals after RYGB also had a large population of Gammaproteobacteria , which were not found in subjects prior to surgery

It is possible that these altered microbiota populations could have a metabolic impact

. It has also been shown that RYGB patients supplemented with probiotics had increased percent excess weight loss

The impact of microbiota on outcomes after RYGB and obesity and metabolism is not fully understood and deserves further exploration

Summary

- Obesity increases the chance for type -2 Diabetes
- Bariatric surgery has proven to improve and resolve type -2 Diabetes
- Mechanisms include calorie restriction, weight loss and hormonal manipulation through altering the anatomy of the G I tract