Surgical Treatment of Type 2 Diabetes

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Disclosure

* None
Objectives

* Define DM2 and its causes
* Describe link with obesity and DM2
* Identify how major bariatric operations affect DM2
* Compare medical to surgical treatment of DM2
* When should patients with DM2 be referred for surgery?
Definition of Pre Diabetes

* FBS=100-125
* RBS= 140-149
* Impaired GTT
* Hgb A1c=5.7-6.4
* 25% of Pre-diabetic become diabetic in 3-5 years
Definition of DM

* Random serum glucose > 200
* Fasting glucose > 120
* 2 Hr. post prandial glucose > 200
* Hgb A1c > 6.5%
Causes of DM1

* Autoimmune disease that occurs when T cells attack and decimate beta cells (insulin producing) in the pancreas.
* Tends to occur in childhood, adolescence or early adulthood (before age 30) but may have clinical onset at any age.
* Only 5-10% of Diabetics
* Polydypsia, polyuria, polyphagia
* Can lead to blindness, CRF, neuropathy, accelerated atherosclerosis
* Requires insulin for treatment
Who was the first scientist to isolate insulin and treat hyperglycemia in pancreatectomized dogs?

Answer: Toronto surgeon, Frederick Banting, 1921 winning the Nobel prize in 1923
* 90-95% of Diabetics
* Impaired insulin secretion combined with Insulin resistance
* Disposition Index- Product of secretion and sensitivity in response to blood sugar levels- measure of beta cell function.
* Lowering of the Di predicts conversion of IR to DM2
* Both contributed to by genetics and environment
* Leads to impaired glucose tolerance
* Leading to DM 2
* Beta cell failure occurs as time passes
Causes of DM2

- Strong association with morbid obesity, poor diet and inadequate exercise
- High fat diets tend to be associated with insulin resistance, particularly with respect to saturated fat and trans fatty acids.
- Protein ingestion stimulates insulin secretion.
- Dietary fiber has indirect effects on insulin secretion and action.
- High carbohydrate diets are generally associated with improved insulin sensitivity in the short term but this depends on the type and physical form that carbohydrates are consumed.
- The glycemic index (GI) of a food refers to the area under the curve for blood glucose concentration versus time, relative to an equivalent dose of glucose.
- Low glycemic carbohydrates better than high
- Epidemiological studies such as the US Physicians Health Study have reported substantial decreases in the relative risk of type 2 diabetes with lifelong regular physical activity.

Insulin resistance increases with increasing body mass index, waist circumference and in particular waist-hip ratio.95 or greater.

These reflect increased adiposity especially increased levels of visceral adipose tissue.

Visceral adipose tissue refers to intra-abdominal fat around the intestines and correlates with liver fat.

Visceral adipose tissue has metabolic characteristics which differ from that of subcutaneous fat.

It is more metabolically active with regard to free fatty acid turnover; the increased flux of free fatty acids promotes insulin resistance at a cellular level and increases hepatic VLDL production.

Adipose tissue produces cytokines which have been associated with insulin resistance

* TNF (tumor necrosis factor alpha)
* Interleukins
* PAI-1 (plasminogen activator inhibitor-1)
* High association with obesity (20-25% of patients undergoing bariatric surgery) 22% in personal series
* USA is 3rd leading country affected by diabetes (#1. India #2. China)
* Known as “Adult Onset” DM in the past but now very commonly seen in obese children with 1/3 children born today becoming diabetic prior to adulthood
* “Diabesity”
Link to Obesity
* Who was the first scientist that identified that increased adipose tissue (especially in the upper body, “android”deposition) was associated with diabetes and vascular disease?

* Answer: French endocrinologist, Jean Vague, 1956

Defining Remission

* Partial remission = Hgb A1C up to 6.5, FBS 100-125
* Complete remission = Hgb A1C < 6, FBS < 100 at least 1 year off medications.
* Prolonged remission = > 5 years

American Diabetes Association (ADA), 2009
**Surgical Treatment of DM2**

* Bariatric Surgery = Metabolic Surgery
* ASBS changes its name to the ASMBS in 2007
* Criteria qualifying patients for bariatric surgery include both weight alone (BMI = 40) and the association with significant health problems (BMI = 35-39) with co-morbidities
* One of the chief being DM2
Categories of Bariatric Operations

* Restrictive
* Malabsorptive
* Combined
* Adjustable Gastric Banding (AGB)
* Sleeve Gastrectomy
* Roux en Y Gastric Bypass (LRYGB)
* Biliopancreatic Diversion with Duodenal Switch (BPD-DS)
Adjustable Gastric Banding
* Strictly through the mechanism of weight loss by restriction/satiety?
* Necessary to promote high protein, low fat, low carb diet for maximal effect.
Randomized 60 obese participants with BMIs of 30-40 kg/m² and a recent diagnosis of type 2 diabetes (< 2 years) to either AGB or conventional medical therapy.

The primary endpoint was the rate of diabetes remission at 2 years, defined as a fasting glucose of < 126 mg/dl and an A1C of < 6.2% in the absence of anti-diabetic medications. (ADA partial remission)

Conventional medical therapy consisted of visits every 6 weeks with at least one member of the medical team, which included a general physician, nurse, diabetes educator, and dietitian, for the duration of the trial.

Pharmacological therapy was determined on an individual basis by a diabetologist, and all participants in this group received individual counseling about lifestyle modification.

Fifty-five participants (92%) completed follow-up at 2 years.

Twenty-two of 30 participants (73%) in the surgical group achieved the primary endpoint compared to 4 of 30 (13%) in the medical therapy group.

Surgical and conventional therapy groups lost a mean of 20.7 and 1.7% of initial body weight, respectively.

* Poor long term weight loss
* Recurrence of diabetes
* Complications: Slip, Erosion, Device malfunction, Band obstruction, GERD
* Reoperation 8-60%
Sleeve Gastrectomy and DM2
* Retrospective review of 30 patients with DM between 2005-2007
* 2 and 6 months follow up with impact on Hgb A1C, FBS and BMI
* 22 patients (73%) were taking meds for DM2 preoperatively
* 27% resolved their DM2 at 2 months with Hgb A1C6.36+-.82 preop to 6.02 ±.57 (n=11)
* 63% resolved in 6 months with Hgb A1C=5.92 ±.33 (n=12)
* BMI 46.12 ± 10.86 (n=30) preop
* BMI=38.27 ± 6.59 (n=30) at 2 months
* BMI=35.78 ± 5.11 (n=29) at 6 months
* Patients with a shorter duration of DM (<5 yr) and better weight loss after surgery achieved greater resolution rates.
* Conclusion: The improvement and resolution of DM in obese patients has been observed as a result of weight loss after sleeve gastrectomy.
* Is gastric emptying decreased or increased after sleeve gastrectomy?

* Answer: increased. In fact gut transit time is more rapid until terminal ileum which then slows emptying into cecum as compared to preoperatively.
Ninety-one patients who underwent LSG were investigated. Insulin secretion (insulinogenic index [IGI]), insulin resistance, plasma glucose level and percentage of Hgb A1C using the oral glucose tolerance test were assessed before surgery, on postoperative day 3, and then at 6, 12, 24, and 36 months after LSG. At the same time points, WL, ghrelin, and GLP-1 levels were determined. During follow-up, the resolution rate of type 2 diabetes was 9.4%, 42.3%, 71.8%, 81.2%, and 91.8%, respectively. Ghrelin plasma concentrations decreased significantly after LSG (271.5 ± 24.5 pg/mL versus 122.4 ± 23.4 pg/mL, \( P = .04 \)). GLP-1 plasma concentrations increased significantly after LSG (1.7 ± 2.6 pg/mL versus 2.5 ± 3.4 pg/mL, \( P = .04 \)). LSG may affect glucose homeostasis by 2 different time-related modes: a first step in which the hormonal changes play a predominant role in glucose homeostasis and a second step in which the percentage excess weight loss determines the metabolic results.
Bariatric operations that deliver nutrients to distal small intestine promote secretion of gut peptides.

Gut peptides, which mediate the enteroinsulinlar axis, include the incretins, glucagon-like peptide-1 (GLP1) and glucose-dependent insulinitropic peptide (GIP), as well as ghrelin and peptide YY

Results in enhanced insulin secretion and sensitivity.

* Potent satiety signal and insulin secretagogue, is secreted by the L cells of the distal ileum in response to nutrients and neural signals arising from the proximal gut.

* GLP-1 acts directly on pancreatic β-cells to enhance glucose-dependent insulin secretion. It also suppresses glucagon secretion.

* GLP-1 attenuates postprandial glycemia by slowing gastric emptying and exerts additional effects on the central nervous system to induce satiety and decrease food intake.

Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007;87:1409-1439
Gastric inhibitory polypeptide (GIP) or gastroinhibitory peptide, also known as the glucose-dependent insulinotropic peptide, is an inhibiting hormone of the secretin family of hormones.

- Secreted by the K cells of the proximal gut in response to the ingestion of carbohydrates and lipids.
- Although less potent than GLP-1, GIP also acts on pancreatic β-cells to augment postprandial insulin secretion.
- Variable response after bariatric surgery
- While it is weak inhibitor of gastric acid secretion, its main role is to stimulate insulin secretion

Meier JJ, Nauck MA, Schmidt WE, Gallwitz B.
Gastric inhibitory polypeptide: the neglected incretin revisited
This peptide is a satiety signal that is co-secreted with GLP-1 from the L cells of the distal ileum in response to nutrients.

- Decreases appetite through central mechanisms.

- Indirectly affects glucose homeostasis through activation of melanocortin neurons in the hypothalamus that affect insulin sensitivity.


* Orexigenic hormone is primarily secreted by the gastric fundus and proximal small intestine and acts on the hypothalamus to stimulate appetite.
* Decreasing Ghrelin contributes to the marked loss of appetite and reduction in food intake.
* Ghrelin is known to inhibit insulin secretion. Enhance insulin sensitivity.
* Because ghrelin inhibits insulin secretion, suppresses the insulin-sensitizing hormone adiponectin, and stimulates the release of counter regulatory hormones, a reduction in ghrelin secretion may have beneficial effects on glucose homeostasis.

LRYGB and DM2
Randomized, nonblinded, single-center trial,
Intensive medical therapy alone versus medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy.
150 obese patients with uncontrolled type 2 diabetes.
The average glycated hemoglobin level was 9.2±1.5%.
The primary end point was the proportion of patients with a glycated hemoglobin level of 6.0% or less 12 months after treatment.
93% completed 12 months of follow-up.
12% (5 of 41 patients) in the medical-therapy group achieved primary end point
42% (21 of 50 patients) in the gastric-bypass group (P=0.002)
37% (18 of 49 patients) in the sleeve-gastrectomy group (P=0.008).
Weight loss was greater in the gastric-bypass group and sleeve-gastrectomy group (−29.4±9.0 kg and −25.1±8.5 kg, respectively) than in the medical-therapy group (−5.4±8.0 kg) (P<0.001 for both comparisons).
The use of drugs to lower glucose, lipid, and blood-pressure levels decreased significantly after both surgical procedures but increased in patients receiving medical therapy only.

Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes
Outcomes 5 years after 150 patients who had type 2 diabetes and a body-mass of 27 to 43 were randomly assigned to receive intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary outcome was a glycated hemoglobin level of 6.0% or less with or without the use of diabetes medications.

RESULTS:
- Of the 150 patients who underwent randomization, 1 patient died during the 5-year follow-up period;
- 134 of the remaining 149 patients (90%) completed 5 years of follow-up.
- At baseline, the mean (±SD) age of the 134 patients was 49±8 years, 66% were women, the mean glycated hemoglobin level was 9.2±1.5%, and the mean BMI was 37±3.5.
- At 5 years, the criterion for the primary end point was met by 2 of 38 patients (5%) who received medical therapy alone,
- 14 of 49 patients (29%) who underwent gastric bypass (unadjusted P=0.01, adjusted P=0.03, P=0.08 in the intention-to-treat analysis)
- 11 of 47 patients (23%) who underwent sleeve gastrectomy (unadjusted P=0.03, adjusted P=0.07, P=0.17 in the intention-to-treat analysis).
- Patients who underwent surgical procedures had a greater mean percentage reduction from baseline in glycated hemoglobin level than did patients who received medical therapy alone (2.1% vs. 0.3%, P=0.003)

Schauer PR1, Bhatt DL1, Kirwan JP1, Wolski K1, Aminian A1, Brethauer SA1, Navaneethan SD1, Singh RP1, Pothier CE1, Nissen SE1, Kashyap SR1; STAMPEDE Investigators.
At 5 years, changes from baseline observed in the gastric-bypass and sleeve-gastrectomy groups were superior to the changes seen in the medical-therapy group with respect to body weight (-23%, -19%, and -5% in the gastric-bypass, sleeve-gastrectomy, and medical-therapy groups, respectively), triglyceride level (-40%, -29%, and -8%), high-density lipoprotein cholesterol level (32%, 30%, and 7%), use of insulin (-35%, -34%, and -13%), and quality-of-life measures (general health score increases of 17, 16, and 0.3; scores on the RAND 36-Item Health Survey ranged from 0 to 100, with higher scores indicating better health) (P<0.05 for all comparisons). No major late surgical complications were reported except for one reoperation.

**CONCLUSIONS:**

Five-year outcome data showed that, among patients with type 2 diabetes and a BMI of 27 to 43, bariatric surgery plus intensive medical therapy was more effective than intensive medical therapy alone in decreasing, or in some cases resolving, hyperglycemia. (Funded by Ethicon Endo-Surgery and others; STAMPEDE ClinicalTrials.gov number, N Engl J Med. 2017 Feb 16;376(7):641-651. doi: 10.1056/NEJMoa1600869. Schauer PR1, Bhatt DL1, Kirwan JP1, Wolski K1, Aminian A1, Brethauer SA1, Navaneethan SD1, Singh RP1, Pothier CE1, Nissen SE1, Kashyap SR1; STAMPEDE Investigators.)
DS and DM2
DS and DM2

* Greatest and most durable weight loss
* Greatest effect on DM2
Single-center, nonblinded, randomized, controlled trial, 60 patients between the ages of 30 and 60 years with BMI of 35 or more, a history of at least 5 years of diabetes, and a glycated hemoglobin level of 7.0% or more (8.65±1.45%). Randomly assigned to receive conventional medical therapy or undergo either gastric bypass or biliopancreatic diversion. 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 HgbA1C <6.5% in the absence of pharmacologic therapy). 0 remissions in the medical-therapy group (7.69±0.57% avg Hgb A1C) 75% in the gastric-bypass group (6.35±1.42% avg Hgb A1C) 95% in the biliopancreatic-diversion group (4.95±0.49% avg Hgb A1C) Age, sex, baseline BMI, duration of diabetes, and weight changes were not significant predictors of diabetes remission at 2 years or of improvement in glycemia at 1 and 3 months.

Summary of effect of different bariatric operations on gut hormones and DM2

DS > LRYGB > Sleeve > AGB

* Ghrelin  (-)  (-)  (-)  (+)
* GLP1    (++) (++) (+) (0)
* PYY1    (?)  (++) (+/-) (0)
* GIP     (+)  (+-) (?) (0)

Bariatric surgery versus conventional medical therapy for type 2 diabetes.
Investigational operations on the non morbidly obese

* Duodenal-Jejunal bypass
* Ileal Transposition
* Endoscopic duodenal-jejunal sleeve
Metabolic surgery should be recommended as an option to treat type 2 diabetes in appropriate surgical candidates with BMI ≥40 kg/m² (BMI ≥37.5 kg/m² in Asian Americans) and in adults with BMI 35.0-39.9 kg/m² (32.5-37.4 kg/m² in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with reasonable nonsurgical methods. A

Metabolic surgery may be considered as an option for adults with type 2 diabetes and BMI 30.0-34.9 kg/m² (27.5-32.4 kg/m² in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with reasonable nonsurgical methods. A

Metabolic surgery should be performed in high-volume centers with multidisciplinary teams that understand and are experienced in the management of diabetes and gastrointestinal surgery. C

Long-term lifestyle support and routine monitoring of micronutrient and nutritional status must be provided to patients after surgery, according to guidelines for postoperative management of metabolic surgery by national and international professional societies. C

People presenting for metabolic surgery should receive a comprehensive readiness and mental health assessment. B

People who undergo metabolic surgery should be evaluated to assess the need for ongoing mental health services to help them adjust to medical and psychosocial changes after surgery. C

American Diabetes Association
Diabetes Care 2019 Jan; 42(Supplement 1): S81-S89.
Conclusions

* Bariatric Surgery = Metabolic Surgery
* Bariatric operations have profound positive effects on DM2 both through weight loss and the entero-insulin axis.
* The sooner (lower BMI, younger, the less time with diagnosis of DM2), the better the outcome.
* Operations that increase delivery to the hindgut have greater effect on DM2.
* Uniformity in reporting results and long term follow up will be required to win over our medical colleagues.
Questions?