GASTROINTESTINAL SURGERY FOR NON-OBESE DIABETICS TYPE 2

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SUMMARY

Based on some bariatric operations and animal findings, there are some evidences that rerouting the food through the digestive tract may lead to an improvement of type 2 Diabetes Mellitus. Knowing that around 60% of the diabetic population have a BMI below 35, thus not included in the classical indications for bariatric surgery, it was decided to study in humans, if the same principles of diabetes control, without strong relation to weight loss, could result in the same good outcomes regarding diabetes control obtained in the obese population. The results were surprisingly exciting. Although in its infancy, diabetes surgery have a great potential to stay in the armamentarium of the medical community to manage this progressive and devastating disease.

Key words: Metabolic Surgery; Type 2 Diabetes; Gastrointestinal Surgery.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major cause of death in the world given its relation to kidney failure, blindness, amputations, heart attack and others as erectile dysfunction, diarrhea and gastroparesis (1). Medical therapy for this disease has advanced considerably but still leaves a majority of patients susceptible to its severe effects. While new drug therapies continue to improve medical therapy for this disease, a majority never reach the defined targets for success.

RATIONALE FOR THE SURGICAL TREATMENT OF T2DM

A) Results following bariatric surgery

Clinical resolution of T2DM, usually defined as independence from all antidiabetic medications (2), was reported to occur in 48% of patients after adjustable gastric banding (AGB), 84% after Roux-en-Y gastric bypass(RYGB) and 98% after bilio pancreatic diversion (BPD) (3). T2DM resolution in AGB is proportional to weight loss. The remarkable resolution of diabetes after the 2 last mentioned procedures typically occurs too fast to be accounted for by weight loss alone, suggesting that there may have a direct and more profound impact on glucose homeostasis. The antidiabetic effect of bariatric surgery is long lasting. Long-term control of glycemia and normal levels of glycated hemoglobin after RYGB have been documented in large series with up to 14 years of follow up (4).

While T2DM is often associated with obesity, this relationship is highly dependant on geographic location. Interesting to note though, that there are no published studies that show any evidence of obesity as a cause of diabetes. The average BMI of a T2DM patient in the United States is 31 while in India, the average is 27 .Despite its efficacy with respect to weight loss and resolution of co-morbid health conditions, bariatric surgery is in theory, less desirable for normal/overweight

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patients. Bariatric operations have occasionally been performed in non-morbidly obese individuals. Cohen et al.,recently published the surgical treatment of 37 patients outside the standard 1991 NIH surgical indications, with BMIs varying from 32 to 35, all with T2DM among other comorbidities. These patients underwent laparoscopic RYGB and all had remission of their diabetes (5).

The final common pathway of current and past surgical experience with regard to diabetes resolution seems to be duodenal bypass, although there is some degree of swifter food delivery to distal intestine in both RYGB and BPD (6). Eventually, amelioration of T2DM can be accounted for by the well-known effect of weight loss to increase insulin sensitivity, thereby decreasing glucotoxicity and lipotoxicity and improving β-cell function, but again, T2DM remission usually occurs days or weeks after RYGB or BPD.

So, if T2DM resolution happens long before considerable weight loss, it is long lasting, so why not offer it to lower BMI patients?

B) Potential mechanisms for glycemic control

Regardless of the molecular explanation, which still remains to be elucidated, it would be very important to understand which part of the typical anatomical rearrangement of RYGB/BPD is essential for the effect on diabetes. Two mechanisms have been proposed, based on some elegant animal studies (7, 8). The "foregut or upper intestinal mechanism" holds that the exclusion of the duodenum and proximal jejunum from the transit of nutrients may prevent the secretion of a putative signal that promotes insulin resistance and leads to T2DM control. An alternative proposal, the "hindgut or distal intestinal mechanism", justifies T2DM remission as resulting from the expedited delivery of nutrient chyme to the distal intestine, enhancing a physiologic signal that improves glucose metabolism. A potential candidate mediator of this effect is GLP-1 and/or other distal gut peptides. Although no obvious candidate molecules can be identified with current knowledge, if proven true, those theories might open new avenues in the search for the cause and cures of diabetes.

Recently, a French group (10) published a very elegant animal paper comparing the effects over T2DM control in 2 types of surgery, a purely restrictive - gastric banding, and a duodenal exclusion. The duodenal exclusion group specifically reduced food intake and increased insulin sensitivity as measured by endogenous glucose production. Intestinal gluconeogenesis increased after the duodenal exclusion procedure, but not after gastric banding. They provide a mechanistic evidence that rearranging the upper gut anatomy carries a beneficial effect on food intake and glucose homeostasis involving intestinal gluconeogenesis independent of GLP1 levels or weight change. They considered an important heatoportal sensoring pathway.

In 2008, Laferrere et al (14) compared 2 groups of 10 patients each matched to BMI, history of T2DM and weight loss post op and diet. In patients with similar weight loss, they compared the incretin effect in both groups. They concluded that incretin release was 6 times greater in the surgical group and its effect was not related directly to weight loss, but rather to the surgical induced weight loss at 1 month. The animal and Laferrere's findings are excellent clues that incretin effect and potential glucose metabolism control may be not directly related only to weight loss.

Cure, control or remission?

Type 2 Diabetes has a very complex pathophysiology. It includes inadequate hepatic glucose production, genetics, pancreatic amyloid deposition, insulin resistance, lack of incretin effect through several mechanisms among others. As it's so hard to fully understand all mechanisms related to how surgery may contribute to improve T2DM, cure should never be used when describing the postoperative outcomes. Control or remission seem to more adequate. Surgery, as all other forms of treatment should be interpreted as complementary and not exclusive therapies. It should never be forgotten that some drugs and even insulin may be very helpful in achieving T2DM control, mainly in the early postop. Among them, metformin, pioglitazone and sulphonylureas may be necessary to help mantain good blood glucose levels.

Recent human reports

a) Duodenal jejunal bypass (DJB) (Figure 1): Cohen et al. (9) published in early 2007, a step toward extending animal studies' findings into the clinical arena, reporting 2 cases of persons with diabetes who underwent a DJB. The patients were overweight or mildly obese, with BMIs of 29 and 30.3 kg/m2. Their diabetes was not particularly longstanding (2 and 7 years, respectively), and it was

FIGURE 1. LAPAROSCOPIC DUODENAL JEJUNAL BYPASS

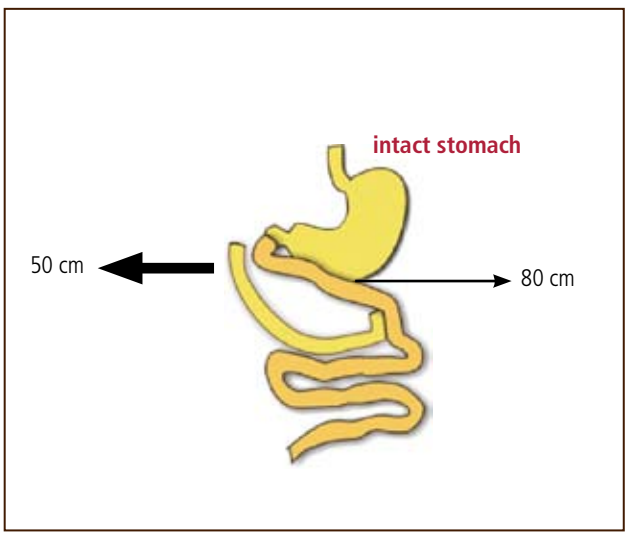


Figure 1. "Classic "(non sleeved) duodenal jejunal bypass

treated before surgery with insulin plus metformin in one case, and with rosiglitazone in the other. Although no preoperative laboratory data were shown, evaluations at one week, one month, and thereafter at monthly intervals for 9 months, demonstrated rapid and unequivocal improvements in several simple measures of glucose control. Fasting blood sugars were initially in the diabetic range (148 and 178 mg/dL), but they decreased steadily after surgery, reaching nondiabetic values by 1 month and remaining at 100 mg/dL throughout postoperative months 3 through 9. Similarly, fasting insulin levels started high (27 and 29 mmol/L) but declined quickly and progressively after surgery, remaining at levels typical of persons without diabetes (approximately 5 mmol/L) throughout postoperative months 3 through 9. Reflecting the improvement in glycemia, hemoglobin A1c values fell from diabetic (8%-9%) to normal (5%-6%) values by 3 months, and they remained equally low thereafter during the remaining 6 months of observation. One patient was discharged a few days after surgery without any diabetes medications, and the other had discontinued diabetes medications by 5 weeks after surgery. In short, both patients converted from having poorly controlled diabetes, despite being on medications, to having normoglycemia off of all such medications. A key finding was that this salutary transformation occurred with no weight loss in either patient.

To describe outcomes, we arbitrarily followed the criteria as in Table 1. So far, 86 patients wee submitted to DJB, with BMI ranging from 22 to 34. Those who have had a longer follow-up - 12 months - have shown 78% between remission and improvement of type 2 DM, regardless of weight loss or gain. There is no doubt that these findings are a strong paradigm shift in the treatment of patients with diabetes.

In this series, there have been strong responders-patients without either insulin or medications who actually regained weight after surgery but are still diabetes-free. There is no significant raise of GLP1 levels as well. There are several unanswered questions in the mechanism of action of diabetes control after rearranging the upper GI anatomy.

TABLE 1.

OUTCOMES CLASSIFICATION
• Resolution - No, meds/insulin, HbA1c<7%
• Control - Less meds/no insulin, HbA1c<7%
• Improvement - Less meds/no insulin, HbA1c<baseline
• Non response - Same or worst than baseline

Quality of life, measured through the SF 36, showed high scores in 86% of patients at 6 mo and 80% at 12 mos, mainly related to physical functioning, vitality and social functioning.

But seeking better outcomes in this population, trying to reproduce the results found in class 1 or morbid obesity, we moved forward with some technical /pathophisiological modifications as follows.

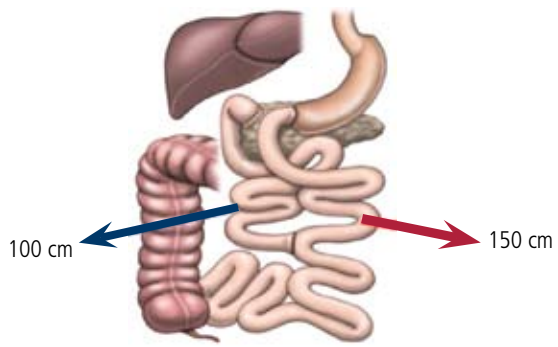
b) Sleeved Duodenal Jejunal Bypass (Figure 2)

Some important clinical trials as ACCORD,ADVANCE and the VA Diabetes trial (15), showed that diabetic patients should be treated targeting not only a tight glycemic control, but all of its comorbidities as well, as hypertension and dyslipidemia. The Steno trial, published in 2008 (16), elegantly demonstrated that intensively focusing on glycemic **and** blood pressure **and** lipid control can bring significant decrease in mortality in the diabetic population.

So based on the aforementioned literature, we decided to conduct our second protocol and performed a "sleeved duodenal exclusion" or a "short duodenal switch", adding a sleeve gastrectomy with a 50 G bougie in 47 patients. The primary endpoints were fasting and postprandial glycemic control and secondary endpoints were lipid, and hypertension control and Carotid Intimal Media Thickness (CIMT), an important marker for atherosclerosis.

Additionally, based on our own studies on limb lengths and diabetes resolution in the superobese population (11), we have increased the billiary limb to 100 cm and the alimentary to 150 cm. Besides our findings, Patti ME, presented in 2007 (17) during the ADA Meeting that after the anatomical modifications following the gastric bypass, there is an altered entero-hepatic circulation of the biliary acids. Patti's data suggests that altered bile acid levels and composition may contribute to improved glucose and lipid metabolism in patients who have had GB with longer biliary limbs.

FIGURE 2. SLEEVED DUODENAL JEJUNAL BYPASS



We believe that ressecting the stomach longitudinally, removing part of the major ghrelin production site, the gastric fundus, may lead to a slower gastric emptying, decreasing the glucose load to the intestine (12,13). Preserving the pylorus is likely to be a key step in decreasing the glycemic peaks after food ingestion, leading to a better first phase insulin response and better glycemic outcomes.

Some authors, mainly basic scientists, described in diabetics, that ghrelin has the biochemical capability to decrease the pancreatic insulin production. So, removing the main ghrelin production site would allow a better control of T2DM.

Adding the sleeve turned the 20% nausea and vomiting incidence rate into virtually zero in the early postoperative period. With an average follow up of 1 year, we found that adding the sleeve gastrectomy and increasing the limbs lengths do not add any weight loss to this leaner group (Total Body weight loss of 6%), and so far there is around 71% of T2DM resolution and control, and 100% if we include patients from remission to improvement. Those figures are exciting, as early after surgery, patients have their diabetes improved, as an implicit direct anti diabetic effect of the surgical procedure. As secondary endpoints, we achieved at 12 months, 67% control of hypertension (normal levels, no medications), triglycerides and LDL cholesterol normalization in 77% and 81% respectively. CIMT was significantly reduced from baseline to 12 months.

Is BMI so important as thought?

There is no doubt that the findings described above are a strong paradigm shift in the treatment of patients with diabetes. In this series, there have been strong responders- patients without either insulin or medications who actually regained weight after surgery but are still diabetes-free. In fact, BMI alone is not an ideal tool to accurately evaluate the risk-benefit ratio in patients with diabetes. Presently, there is no scientific evidence that any clear BMI threshold can distinguish between patients for whom surgery can resolve diabetes and patients in whom surgery would be ineffective.

CONCLUSIONS

Conventional gastrointestinal operations for morbid obesity have been shown to dramatically improve type 2 DM, resulting in normal blood glucose and HbA1c levels with discontinuation of all diabetes-related medications or insulin. Often, the return to fasting euglycemia and normal levels of postprandial and regular insulin levels are observed within days or weeks after surgery, suggesting that weight loss alone cannot entirely explain why surgery improves diabetes. Although there is clear and rapid amelioration of diabetes symptoms, the withdrawal of medication and insulin has to be balanced and slow.

Recent experimental studies illustrate that the rearrangement of the gastrointestinal anatomy is a primary mediator in the surgical control of diabetes. The same outcomes have been reported in humans in investigational trials. These findings raise the possibility that putative mechanisms from the proximal small bowel may be implicated In the pathophysiology of type 2 DM. Together, these data suggest a novel revolutionary concept about an old disease: Type 2 DM may be an operable intestinal illness. As the new trends in diabetes literature, we should aim to randomized controlled trials, surgery for best medical treatment, focusing in glycemic and lipid/blood pressure control. Those trials, besides elucidating the potential role for diabetes surgery, may clarify the best moment for surgical indication.

REFERENCES

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care1998; 21:1414-31.

2. Pories WJ, MacDonald KG, Morgan EJ, e cols.. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. Am J Clin Nutr 1992; 55 (2 Suppl): 582S-585S.

3. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004;292:1724 -37.

4. Pories WJ, Swanson MS, MacDonald KG, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995;222:339 -52

5. Cohen R, Pinheiro JS, Correa JL, Schiavon CA. Laparoscopic Roux-en-Y gastric bypass for BMI <35 kg/m2: a tailored approach Surgery for Obesity and Related Diseases 2006; 2 : 401-404

6. Cummings DE, Overduin J, Foster-Shubert KE, Carlson M - Role of the bypassed proximal intestine in the antidiabetic effects of bariatric surgery. Surgery for Obesity and Related Diseases 3 (2007) 109-115

7. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg 2006;244:741-9.

8. Strader AD, Vahl TP, Jandacek RJ, Woods SC, D'Alessio DA, Seeley RJ. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab 2005;288:E447-53.

9. Cohen R, Schiavon CA, Pinheiro JC, Correa JL, Rubino F. Duodenal-jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22-34 kg/m2: a report of 2 cases. Surg ObesRelat Dis 2007;3: 195-197.

10. Troy S, Soty M,Ribeiro L, laval L,Migrenne S, Fioramonti X, Pillot B, Aubert R, Viollet B, Foretz M, leclerc J,Thorens B, Magnan C, Mithieux

G, Andreeli F -Intestinal Gluconeogenesis Is a Key Factor for Early Metabolic Changes after Gastric Bypass but Not after Gastric Lap-Band in Mice. Cell Metabolism 8, 201-211,, 2008

11. Pinheiro JC, Schiavon CA, Correa JL, Noujaim P, Cohen R - Long-long limb Roux-en-Y gastric bypass is more efficacious in treatment of type 2 diabetes and lipid disorders in super-obese patients. Surg Obes and Relat Dis 4 (2008) 521-525, 2008

12. Broglio F, Arvat E, Benso A, Deghenghi R, Ghigo E - Ghrelin, a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. The Journal of Clinical Endocrinology & Metabolism 86(10):5083-5086, 2001

13. Ariga H, Imai K, Chen C, Mantyh C, Pappas T, Takahashi T - Does ghrelin explain accelerated gastric emptying in the early stages of diabetes mellitus? Am J Physiol Regul Integr Comp Physiol 294: R1807-R1812, 2008

14. Laferrère B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, Kovack, B ,Bawa B, Olivan B - Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes Journal of Clinical Endocrinology & Metabolism, 93(7):2479-85,2008

15. Skyler J, Bergenstal R, Bonow R, Buse J, Howard BV, Kosiborod M, Reaven P, Sherwin RS - Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials . A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association . Diabetes Care 32: 187-192, 2009

16. Gaede P, Lund-Andersen H, Parving HH, Pedersen O - Effect of a multifactorial intervention on mortality in Type 2 diabetes. NEJM 358:580-591, 2008

17. Patti ME, Houten S, Bernier R, Bianco AC, Goldfine A - Gastric bypass surgery increases bile acid levels: Potential contribution to improved glucose tolerance. Poster, American Diabetes Association Meeting, 2007, Chicago, IL

El autor declara no tener conflictos de interés con los laboratorios.