Special lecture from Brazil

Surgery for obese and nonobese diabetics: Worldwide perspectives and Brazilian contributions

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About 220,000 bariatric operations are performed in the USA each year, and 500,000 worldwide, and diabetes affects 30-40% of this population. In addition, 6-10% of overweight and obese patients who are not bariatric candidates (BMI< 35 kg/m2) may be similarly diabetic. (1-3, 5, 15, 16, 19-22).

Response of diabetes mellitus after bariatric weight loss is a time-dependent phenomenon for which total and visceral fat are the principal influence, but where other variables are certainly relevant . Such influences are not static and may change along the years, being compatible with many outcomes, mostly definitive to temporary resolution but also eventual long-term recurrence.

Mechanisms responsible for outcome of obesity-associated diabetes are incompletely defined. Substantial weight loss and resolution of major comorbidities is unquestionable after bariatric interventions for morbid obesity . Clinical course till normalization of glucose as well as mid-term follow-up is reported . However, factors responsible for long-term outcome and possible risk of relapse of diabetes are incompletely defined.

The four principal lines of thought regarding correlates for sustained diabetes regression after RYGB involve BMI /visceral fat reduction, changes of systemic/gastrointestinal hormones, decrease of cytokines and systemic inflammation, and dietary education/remodeling. Most of these have been examined within the short-term perspective, consequently information several years after operation except for BMI is essentially lacking. Three theoretical outcomes can be devised, namely cured patients (long-term remission), persistent or refractory (nonrespondents) , and new-onset diabetes (starting in previously nondiabetic patients).

Incretin expression is increased one month after operation (4) and glucose and insulin normalization reportedly occurs within days , before any weight loss is apparent (5, 6) . Clinical benefit is believed to materialize by the first quarter (6, 7) but subjects may require a longer time to react, and 22% of diabetic candidates are still drug-dependent around one year (8) . Also Perugini et al observed improved fasting glucose and insulin levels as early as after 12 days, but significant additional improvement up to one year was not found (9).

Conflicting reports are more frequent several years after operation. In the experience of Alexandrides et al with type-2 diabetics, even after two years blood glucose was above 110 mg/dL in 34% (10). Proinsulin dramatically diminished by 12 months in the study of Johansson et al, but slightly recovered around 42 months (11).

Food intake and macronutrient composition , not just body composition, are likely to influence long-term findings, but again uneven numbers can be found . Carrasco indicates ingestion of approximately 800 kcal/day (21.3% protein) at six months (4) , similarly to Anderson et al with figures at three months of about 700 kcal/day (37 % protein) and 1100 kcal/day after one year (23% protein) (12) These numbers are consistent with our own experience (2, 23). In contrast the values of Sjostrom et al at six months were in the range of 1500 kcal/day and at 12 months of 1700 kcal/day (13). In between, Bobbioni et al registered nearly 1000 kcal/day (17.9 % protein) at three months, 1140 kcal/day (17.5 % protein) at six months, and 1420 kcal (16.2% protein) by one year (14).

Body mass index is repeatedly linked with diabetes outcome. Even with modern metabolic procedures for diabetes, such as ileal interposition with or without duodenal diversion, good glycemic response occurred simultaneously with rapid weight loss (22% in seven months) and a quite low final BMI (24.9 kg/m2) (15). Much of the difference in long term outcome of malabsorptive versus mixed versus restrictive interventions may be attributed to differences in BMI reduction (13, 16, 17). Thus , it is appealing to ascribe all antidiabetic benefits to calorie restriction and weight loss (18), though that´s clearly not the full answer.

In a preliminary study by our group, which is still going on, operated morbidly obese participants were stratified as responsive diabetes, refractory cases , and never diabetic controls . All underwent gastric bypass (RYGB). Initial BMI was higher in responsive patients but by two years similar values were detected. White blood cell count was also higher in these subjects but refractory cases surpassed them by two years. Baseline lipids were similar in all groups, with less favorable course in refractory subjects (triglycerides, LDL- and HDL-cholesterol) , starting by two years. Blood glucose and HbA1c always tended to be more elevated in the refractory subset. In this sense, age, weight and gender were not relevant for diabetes outcome, dyslipidemia and systemic inflammation correlated with postoperative outcome, and hard to control glucose and HbA1c were also common features of the refractory group (1).

The four principal lines of thought about mechanism for sustained diabetes regression after RYGB are summarized in Table 1.

Table 1: Major hypotheses concerning diabetes surgical response

Variable	Response
1) BMI decrease	70- 90% success after RYGB (Higher for malabsorptive, lower for restrictive operations)(13, 16, 18)
2) Glucose metabolic mediators a)Restoration of insulin sensitivity	 No (19) Yes (20)
b) Insulin secretion	Improved (4, 20)
c) Proinsulin reduction	Yes (11)
d) GIP and GLP-1 secretion	Increased (4, 22)
3) Visceral fat, systemic inflammation, cytokine activation	Decreased adiponectin (21)
4) Dietary calorie and lipid intake	(13, 14, 18, 23, 24)

Hormones have been especially highlighted by recent investigations, though results are still preliminary and often conflicting, as alluded to. Basically a hindgut theory is advanced, in the sense that operations which allow food to quickly reach the ileum would elicit stronger incretin response (GIP, GLP-1). The foregut alternative attributes to duodenal exclusion the role of modulating incretins, perhaps by influencing also their antagonists, the anti-incretins. If the importance of incretins is fairly accepted in metabolic surgery, the same cannot be said about anti-incretins, which have not been surely identified or measured in the surgical context (Table 2).

Table 2: Potential roles of incretins and anti-incretins in the diabetes context

General modulation of diabetes

BMI (weight loss)
Severity of disease (Insulin, HbA1c, duration)
Gastric factor : ghrelin
Duodenal factors: insulin
Pancreatic factors: incretins, anti-incretins
Ileal factors: Incretins, adiponectin
Hindgut theory: increase of incretins (?)
Foregut theory: reduction of anti-incretins (?)

Activity of incretins (GLP1,GIP)

Insulin synthesis and secretion
Beta cell proliferation and apoptosis

Anti-incretins (cytokines IL-1, TNF, IFN, NO, agents causing endoplasmic reticulum stress, oxidative stress)

Suppression of the actions of incretins

Metabolic operations at this moment encompass both innovative techniques and classic bariatric procedures . The first group is currently being conducted in Brazil only, and is composed by ileal interposition (15, 26), duodeno-jejunal exclusion (27, 28), and sleeve gastrectomy, omentectomy and partial enterectomy (Santoro operation) (29). All of them consider both the foregut and the hindgut theories, with variable emphasis on one or the other. Elsewhere conventional interventions have been used for some time, in overweight, obese and morbidly obese candidates (30, 31). Results with a few options are summarized in Table 3 and 4.

One is tempted to belive that tailor-made interventions will be ideal, but outcomes so far have not demonstrated clear superiority of new operations versus classic ones, perhaps because series are still small and populations heterogenous. Prospective controlled trials, with sufficient follow-up period, will be indispensable to sort out the best .

Table 3
Table 4

Table 3: Representative results with new surgical modalities

Modality	DJB (27)	DJB (28)	Ileal interposition (15, 26)
BMI range	<30	<30	21-34
Weight	Reduced and stabilized	No change	Reduced and stabilized
Glucose	44% reduction	14% reduction	40% reduction
HbA1c	22.8% reduction	12% reduction	57.6% remission
Medication	90% free	83% switched to oral	90% free
Population	oral and insulin	Insulin only	Oral and insulin

Table 4: Diabetes response with traditional operations

Modality	RYGB (1)	Various (30)	Various (31)
BMI range	>35	<35	>35
Weight	32% reduction	17.7% reduction	29.7% reduction
Glucose	36.3%	47%	32%
HbA1c	38.1%	31%	
Medication	94% free	85.3% free	61% Band, 81% RYGB and SG
Population	31% Diabetics	Oral and insulin	Oral and insulin

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