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Digestive Adaptation with Intestinal Reserve: A Neuroendocrine-Based Operation for Morbid Obesity

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Background: Mechanical obstacles to food ingestion, nutrient-excluded segments and malabsorption are common strategies of bariatric surgery which are a potential cause of symptoms or complications. We describe an operation "Digestive Adaptation with Intestinal Reserve" (DAIR) that does not utilize these tools, aiming fundamentally at neuroendocrine changes.

Methods: The operation includes sleeve gastrectomy, omentectomy and enterectomy, maintaining the initial 40 cm of jejunum and final 260 cm of ileum (keeping the bowel length at the lower limit for adaptation to normal). Jejunum is laterally anastomosed to ileum 80 cm proximal to the cecum. A gastroileostomy creates a transit bipartition (ileum and proximal bowel in transit). 55 patients are presented whose follow-up is >12 months (12-34 months). Fasting ghrelin and resistin, and postprandial GLP-1 and PYY were measured.

Results: Mean BMI reduction was 4.8, 9.5, 15.4 and 20.1 kg/m^2 respectively at 1, 3, 6 and 12 months. Patients have early satiety and major improvement in pre-surgical co-morbidities, especially diabetes and hypertension. GLP-1 and PYY response to food ingestion were enhanced; fasting ghrelin and resistin were significantly reduced (P<0.05). Radiographic studies show nutrient transit through the pylorus and through the gastroileostomy. Early surgical complications (2 in 55 patients) resolved without sequelae. There were no signals of malabsorption, no deaths, and most patients present no symptoms at all.

Conclusions: DAIR amplifies postprandial neuroendocrine response and provokes intense weight loss. DAIR reduces production of ghrelin and resistin and enables more nutrients to be absorbed distally enhancing GLP-1 and PYY secretion. Diabetes improved significantly without duodenal exclusion.

Key words: Obesity, morbid obesity, ghrelin, resistin, PAI-1, GLP-1, PYY, visceral fat, gastrectomy, omentectomy, enterectomy

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Introduction

Obesity has become a major public health problem. Conservative treatment alone is not sufficient in a significant proportion of patients, and, although many bariatric surgical techniques are available, all current operations present some features that would be better avoided from a strictly physiological point of view, such as the creation of obstacles to food ingestion (prostheses or narrow anastomoses), exclusion of digestive tract segments from nutrient transit and significant nonspecific malabsorption.

Exclusion of digestive segments impedes endoscopic evaluation of the excluded area and may cause structural damage to the mucosa, bacterial proliferation and, possibly, bacterial translocation. Some oper-

ations that involve digestive tract nutrient exclusion have been associated with hepatic fibrosis,[1,2] that may worsen the hepatic condition of patients that frequently present with some degree of nonalcoholic fatty liver disease.[3] Even shorter excluded segments, like in gastric bypass, may lead to hepatic insufficiency.[4]

Here, we report results of 55 patients submitted to a new bariatric operation that was first described in 2004.[5] It is designed to spare the pylorus, duodenum and jejunum from nutrient exclusion. Indeed, our objective was to avoid any nutrient exclusion, blind endoscopic areas, narrow anastomoses and bands, and to minimize or abolish malabsorption. On the other hand, the procedure aims to magnify the neuroendocrine gastrointestinal (GI) response to food ingestion, by suppressing efficiently the orexigenic signals and promptly generating satiety signals.

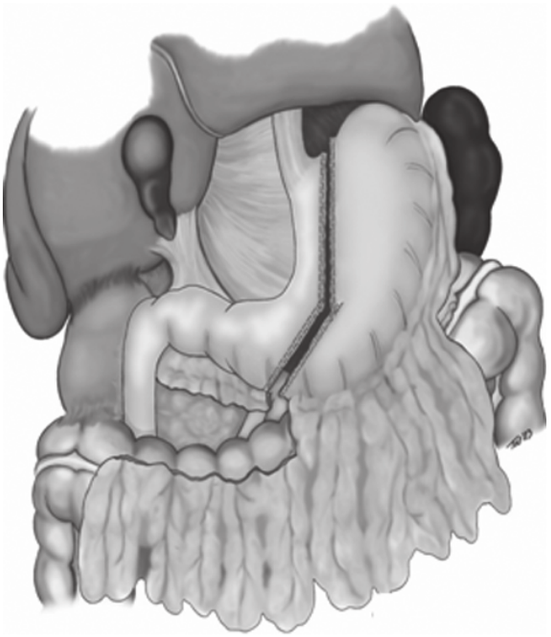

Figure 1. Diagram showing the dimensions of the sleeve gastrectomy.

Materials and Methods

This proposed surgical procedure combines many aspects of preexisting procedures, although it creates a new concept that is the Intestinal Transit Bipartition; in other words, it creates a biliopancreatic diversion (BPD) but just partially, leaving an open duodenum. The procedure begins through a laparoscopic access. Five trocars are positioned: two 12-mm (one in the midline 8 cm above the umbilicus and the other in the left upper quadrant); and three 5-mm trocars (one in the right upper quadrant, one in the epigastrium for the liver retractor and one lateral in the left upper quadrant).

First, the omental bursa is opened and section of the greater omentum is done using a sealer and divider device (Ultracision® or Ligasure®). Dissection starts just beside the gastric greater curvature at a point 4 to 6 cm proximal to the pylorus up to the angle of His. A sleeve gastrectomy is performed with a laparoscopic linear cutting stapler (Figure 1). A Fouchet's tube is passed to the stomach and positioned on the lesser curvature, to guarantee that the gastric tube, is approximately 3 cm wide. After that, a 10 to 12 cm midline laparotomy is performed to remove the gastric specimen and the greater omentum (after detaching it from the colon) and to perform an enterectomy, leaving the first 40 cm of jejunum and the last 260 cm of ileum.

Jejunum is laterally anastomosed to the ileum 80 cm proximal to the ileocecal valve, and the proximal end of the ileum is anastomosed to the lower limit of the staple-line in the stomach, in a antecolic position (Figure 2). The mesenteric borders are closed to avoid internal hernias. Abdominal wall and laparoscopic incisions are closed. Antibiotic and deep vein thrombosis prophylaxes have been used (cephalothin 1 g q6h for 1 day, pulsatile anti-thrombosis boots, enoxiparin 40 mg once daily until discharge only).

Among the group, 8 consecutive patients (4/4 male/female; mean age 44 years old, mean BMI 46.5 kg/m^2) were submitted to hormonal studies pre and postoperatively. Ghrelin and resistin fasting levels were drawn. Glucagon-like peptide 1 (GLP-1) and polypeptide $YY_{3\text{-}36}$ ($PYY_{3\text{-}36}$) were measured after a 12-hour fast and also 30, 60, 90 and 120 minutes after ingestion of a 300 Kcal standard meal (200 mL of Nutridrink®, Nutricia, Bornem, Belgium). All determinations were made using ELISA kits (Phoenix Pharmaceuticals, Belmont, CA, USA). Results are given as mean ± SD. The nonparametric Wilcoxon Signed-Rank test was used to estimate the difference between pre- and post-procedure. $P<0.05$ was considered statistically significant. Statistical analyses were conducted using the SAS® System (SAS Institute, Cary, NC).

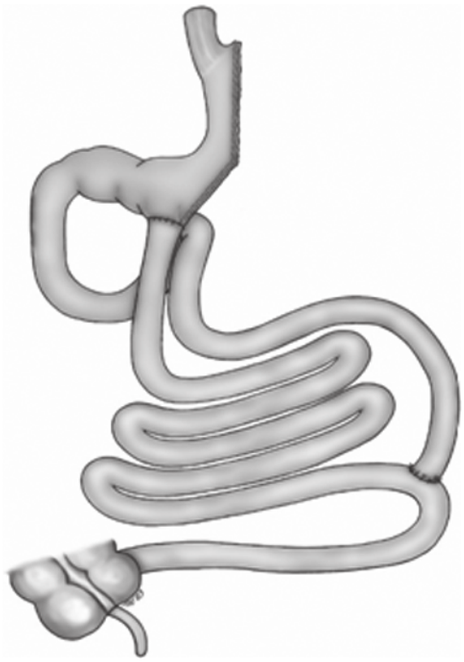

Figure 2. General arrangement of the digestive tract after the operation.

Patients were kept fasting on the first postoperative day; afterward, liquid fractioned meals were offered for 1 week. Then soft solid meals were allowed. Patients were educated to start meals with a portion of varied salad enriched with protein (tuna, salmon, or chicken). Avoidance of refined sugar was advised. Patients were told to limit ingestion of refined white flour and caloric liquids, while vegetables, fruits and water were recommended. They were advised to enroll in a physical activity program that was geared to become more intense as the weight loss occurred. Multivitamins and pantoprazol were prescribed for the first 2 months.

The Ethics Committee of the "Hospital da Policia Militar do Estado de São Paulo" approved the first protocol. The procedure was reviewed and also approved by the Ethics Committee for Research Projects Analysis of "Hospital das Clínicas", School of Medicine of the University of São Paulo. A detailed informed consent was signed by patients or by responsible relatives.

Patients

Only patients with a 1-year follow-up were included. Fifty-five patients were enrolled and operated between June 2003 and May 2005. There were 19 men (34.5%) and 36 women (65.5%), with ages from 14 to 61 years (average 42.5 years).

At the time of study enrollment, patients weighed from 86 to 219 kg (average 124.2 kg), were 145 to 188 cm tall (average 165 cm) and had body mass index (BMI) at the time of the operation from 38 to 72 kg/m^2 (average 45 kg/m^2) and past maximum BMI from 39 to 100 kg/m^2 (average 49 kg/m^2). Diagnosed co-morbidities included orthopedic problems, including articular pain in 32 patients (58.2%), hypertension in 24 (43.6%), diabetes in 26 (47.3%), dyslipidemia in 33 (60%), and respiratory problems in 14 (25.5%).

Clinical Results

Length of operative procedures ranged from 180 to 350 minutes (average 245 minutes). In general, patients were discharged on the 3rd postoperative day (POD). Resected specimen characteristics are shown in Table 1. Early postoperative complications occurred in only two patients (3.6%). One developed sepsis and presented a perisplenic abscess (*Staphylococcus aureus*) surgically drained on the 26th POD.The patient then had a good recovery. The other patient presented a gastric leak after intense vomiting, which was surgically revised and drained on the 3rd POD, also with a good result. There were no deaths.

Late complications included 3 incisional hernias (5.5%) and 4 subjects developed gallbladder lithiasis (7.2%). Mild constipation was observed in some patients, especially in the first 4 months. After that, most patients maintained the same bowel movement frequency observed before surgery. Two still present mild constipation. Some patients noted mild diarrhea eventually.

Table 1. Characteristics of specimens resected from all patients

Organ	Length (average)	Weight (average)	Volume (average)
stomach	-	85-210 g (140)	1.2-2.2 L (1.4)
small bowel	190-480 cm (280)	450-1300 g (700)	-
omentum	-	120-1200 g (830)	-

Only one patient developed, diarrhea that required medication 11 months after the operation. GI series showed that the pylorus was much higher than the gastroileo-anastomosis and the flow to the duodenum was almost zero, creating a total BPD. As this patient had already lost 65 kg and developed cholelithiasis, 8 months ago she was submitted to a cholecystectomy and reversal of the partial BPD (jejunoileal end-to-end anastomosis). However, with the vertical gastrectomy, omentectomy and partial enterectomy alone, she regained only 4 kg and stabilized.

There have been no significant signals of malabsorption. Albumin, calcium, parathyroid hormone, folate, vitamin B_{12} and hemoglobin have been maintained within normal ranges in all patients.

The longest follow-up is 34 months (average 16 months). The average BMI reduction has been 4.8 at 1 month postoperatively, 7.1 at 2 months, 9.5 at 3 months, 12.9 at 4 months, 15.4 at 6 months and 20.1 at 1 year. Patients lose weight slowly in the second year or stabilize. Patients have not yet shown weight regain.

The co-morbidities detected before surgical treatment showed clinical resolution or improvement (Table 2). Resolution was defined as the disappearance of the problem or the withdrawal of medication. Improvement was defined as a reduction in medication or an improvement in objective laboratory results or symptoms. None of the patients operated on failed to improve.

Overall, patients reported a great reduction in total daily ingestion and early and prolonged satiety that is even more intense when fat is consumed. No dumping has been observed. All 55 patients are very satisfied with having undergone the operation.

Table 2. Clinical resolution and improvement of co-morbidities after surgical treatment

Condition	Pre-op (n)	Resolved after surgery	Improved after surgery
Orthopedic problems	32	29 (90.6%)	3 (9.4%)
Hypertension	24	21 (87.5%)	3 (12.5%)
Diabetes	26	24 (92.3%)	2 (7.7%)
Dyslipidemia	33	25 (75.8%)	8 (24.2%)
Respiratory problems	14	13 (92.9%)	1 (7.1%)

Hormonal Assays Results

Among the 55 patients, 8 consecutive patients were submitted to pre- and 2-months postoperative hormonal studies. As expected, fasting ghrelin fell after the procedure in all patients. Preoperative serum levels ranged from 432 pmol/L to 891 pmol/L (mean 653.5 pmol/L; median 621.5 pmol/L; SD 175 pmol/L).

Postoperative values ranged from 106 pmol/L to 275 pmol/L (mean 210 pmol/L; median 213 pmol/L; SD 21 pmol/L). The fall in ghrelin (Figure 3) was statistically significant (P=0.007).

PYY_{3-36} and GLP-1 secretion were enhanced in all patients. Average levels at fasting, and 30, 60, 90 and 120 minutes after a standard meal were invariably higher in the postoperative period than preoperatively for both hormones.

Mean preoperative PYY_{3-36} was 15 pmol/L (median 16.5; SD 5.2). In the postoperative period, average was 24 pmol/L (median 24.5; SD 8.3). This difference was statistically significant (P=0.015), as shown in Figure 3.

Mean GLP-1 level before operation was 14.4 pmol/L (median 14.5; SD 2.3). Postoperatively, mean was 18.2 pmol/L (median 19.0; SD: 4.5). This difference was not quite significant (P=0.07) (Figure 3).

Resistin levels were significantly diminished in all patients. Preoperative values ranged from 15 to 32 ng/mL (mean 25.8; median 26.0; SD 5.3). In the postoperative period, resistin ranged from 11 to 19 ng/ml (mean 15.1 ng/ml; median 15.5 ng/ml; SD 2.5 ng/ml). This difference was statistically significant (P=0.007) (Figure 3).

Discussion

The postprandial deficiency in the production of distal small-bowel hormones, mainly PYY_{3-36} and GLP-1, is being considered as an important issue in the pathogenesis of obesity and related diseases.[6-8] An evolutionary factor may be involved with this. We have recently hypothesized that the long length of human small bowel is an evolutionary remnant developed for a calorie-poor and fiber-rich diet and is not adapted to the modern diet.[9] The primitive diet was hypocaloric and full of poorly digestible fiber. A primitive hominid would have to ingest

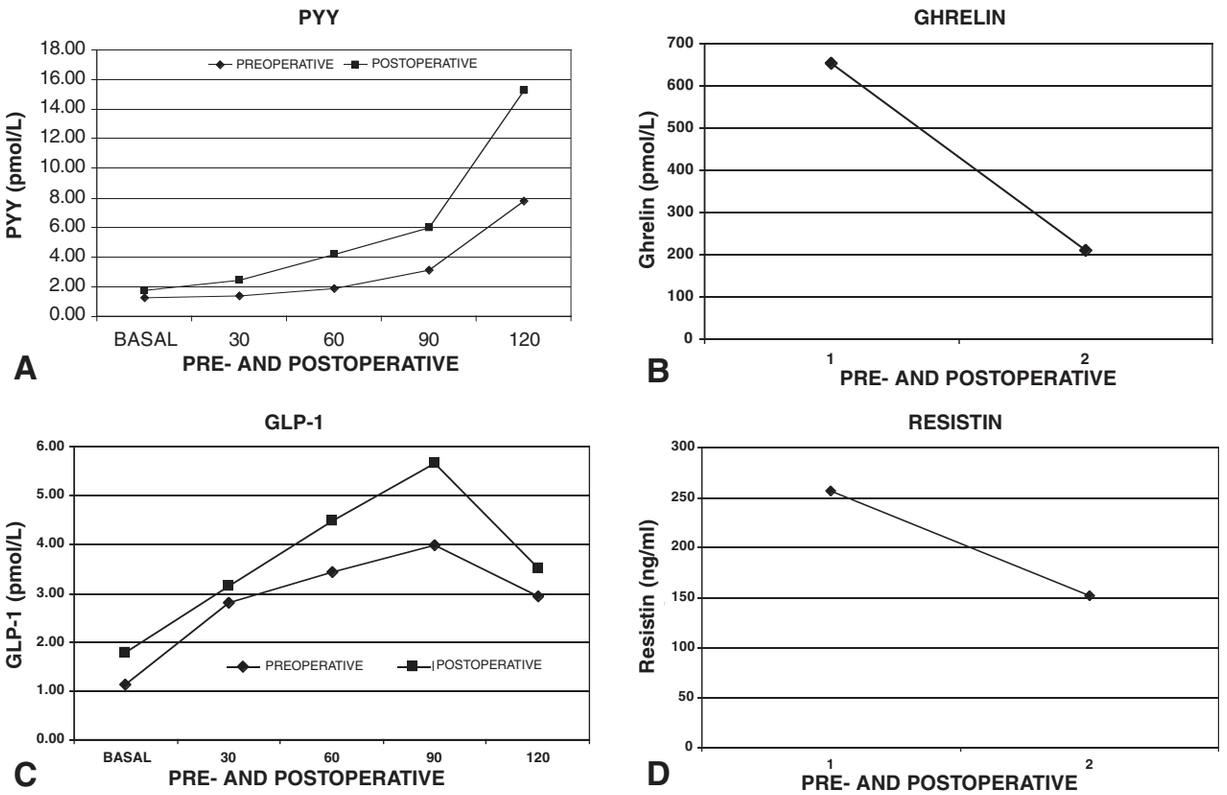

Figure 3. A) Pre- and postoperative average PYY levels comparison at 0, 30, 60, 90 and 120 minutes (*P*=0.015). B) Comparison of average fasting ghrelin levels pre- and postoperatively (pmol/L), *P*=0.007. C) Pre- and postoperative average GLP-1 levels comparison at 0, 30, 60, 90 and 120 minutes (*P*=0.07). D) Resistin pre- and postoperative averages comparison (*P*=0.007).

large food volumes to obtain just a small amount of calories. A large stomach and a long bowel were important as containers, but they also provided the opportunity for absorption of all nutrients among the fiber and indigestible particles. On this voluminous and hypocaloric primitive diet, nutrients would reach distal bowel more easily.

The modern diet consists of concentrated highly absorbable nutrients (including unnatural elements such as refined sugar and white flour), with progressively less fiber and residues. It is possible to efficiently absorb these nutrients in the very first portions of the intestine, thereby creating peaks of nutrient absorption and an "empty distal gut". Nutrient-induced secretion of enterohormones produced by the distal small bowel would be attenuated in this scenario.

Glucagon-like peptide 1 (GLP-1) is a polypeptide hormone that is secreted from the enteroendocrine L-cells of the distal gut in response to nutrients in the lumen.[10] GLP-1 causes potent stimulation of insulin biosynthesis and release from pancreatic beta-cells (potent enough to potentially cure type II diabetes),[11] it reduces gastric acid output,[12] and it causes major reduction in gastric emptying.[13] Also, GLP-1 causes relaxation of the gastric fundus, allowing the stomach to contain a larger volume without increase in distension sensation.[14] Finally, GLP-1 passes through the blood-brain barrier and causes satiety.[15]

Polypeptide YY (PYY) and oxyntomodulin are also gut hormones involved in the response to food ingestion. PYY is found in two forms PYY_{1-36} and PYY_{3-36}. PYY_{3-36} is more specific to Y_2 receptors in the hypothalamus.[16] They are released also by L-cells in the gut in response to food ingestion and cause satiety.[17,18] The obese have reduced basal and meal-stimulated release of PYY.[6]

If the presented theory is correct, beyond the fact that obese people have attenuated secretion of distal small-bowel hormones, it would have to be proven that obese people are able to produce these hor-

mones adequately, if sufficient nutrients reach distal gut. These facts have been demonstrated. Obese,[7] as well as type II diabetic[8] individuals, have attenuated postprandial GLP-1 secretion. The same happens with PYY.[6] Also, immediately and many years after a jejuno-ileal bypass has been performed (which propels nutrients to distal gut through a shortcut), normal GLP-1 secretion is reestablished.[19]

In summary, to have 3 or 8 meters of small bowel (variation of small bowel length among normal adult humans) makes little difference in terms of absorption, because in neither case malabsorption will occur. However, it seems clear that to have nutrients reaching and being absorbed by the distal gut is an important physiological issue, especially in limiting food intake, through the production of intestinal hormones that work as signals to the pancreas and to the brain.

Following this line of reasoning, we could go still further. Obesity has been followed by an increased incidence of colon cancer.[20] Nutrients reaching distal gut provoke secretion of GLP-2 and generation of short-chain fatty acids (SCFA) in the colon, and both GLP-2 and SCFA are thought to be protective against colon cancer.[21,22] Thus, scarcity of nutrients in distal gut could link colon cancer and obesity. Both conditions have increasing incidences in industrialized countries.

These data suggest that, especially if modern, hypercaloric, easily digestible diet is being used, it might be better to have a shorter small bowel. Could the length of small bowel be involved in obesity? Do the obese have a longer small bowel? There have been few studies into this matter, but Hounnou et al[23] have shown that this is the case.

Evolutionary forces have been at work in this matter. Early hominid species were basically herbivores. Glaciations and also appearance of deserts pushed hominids toward a change in diet, by adding animal sources of food. The higher concentration of calories in the meat and the better foraging strategies allowed the Homo groups to eat less volume of more digestible food. It is known that in these transitions the amount of bowel was reduced[24,25] (as expected, because exclusively herbivores have proportionally longer bowel extensions[26]).

During the last century, another great change has occurred in the human diet, which became more concentrated in calories and even freer of non-digestible particles, which has led us to consider that a further GI reduction is now necessary. Evolution continues to perform natural selection. People are becoming obese and dying. Obese people, as Hounnou et al[23] pointed out, have a longer bowel, and thus shorter bowel is being selected.

The "contemporary human being" is insufficiently adapted to the abundance of easily absorbable food. This nutrient excess early in life is a potential stimulus to mucosal hypertrophy in the proximal gut, magnifying its absorptive capacity and attenuating the distal small bowel signals (our nutrient detectors). Nutrient-induced mucosal hypertrophy may be another important issue in this matter. Likewise, the stomach was developed to be a storage chamber of low calorie food. Under the modern diet, the stomach became functionally, too large.

In parallel, our eating instincts were developed under scarcity. Now, we face abundance and a continuous diminution in obligatory physical effort. Obesity and related diseases are the obvious consequences.

Based on this rationale, we have described a surgical strategy to treat obesity that is simply a reduction: Digestive Adaptation[27] (Figure 4). It constitutes vertical (sleeve) gastrectomy, omentectomy and a simple enterectomy that leaves 3 meters of small bowel, mostly ileum. The gastrectomy aims to adapt the size of the gastric chamber to the calorie-

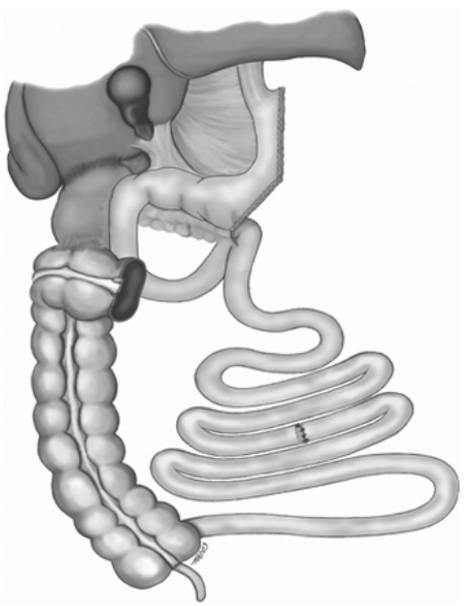

Figure 4. General appearance of the digestive tract after the digestive adaptation[27,29] (vertical gastrectomy, omentectomy, partial enterectomy).

dense modern diet, reducing its volume. Satiety signs caused by distension will be emitted earlier and the main source of ghrelin[28] is removed. The enterectomy does not aim to create malabsorption (this remnant length is the lower limit of normal range; it is completely sufficient for absorption by functional reserve that will be enhanced by intestinal adaptation). Enterectomy is performed to adapt the small bowel to the modern diet, bringing nutrient detectors closer and improving enterohormonal response to ingestion of refined food.

It is a physiological and evolutionary based approach. Two-year results with Digestive Adaptation are excellent.[29] There are now more than 700 patients operated in several Brazilian centers by many surgeons utilizing the same technique (personal communication). However, in heavier patients, an even shorter bowel would probably be more appropriate. Nonetheless, it would not be wise to perform an enterectomy that would leave the patient with an amount of bowel smaller than the lower limit of normal range (although evolution has progressively been lowering this limit).

As we wanted to avoid nutrient exclusions, especially from duodenum, this motivated the development of the technical alternative presented here that was designed mainly for the super-obese, for those who cannot exercise, and perhaps for those with significant gastroesophageal reflux (once most of the parietal cells are removed and the stomach is drained through a gastroentero-anastomosis).

This operation does not involve obstacles to food ingestion, the pylorus remains and the duodenum is in transit. There are no segments excluded from nutrients or from the access of an endoscope (Figure 5). The operation is relatively easy and safe to perform. It may prevent bacterial proliferation and the eventual translocation to portal blood, preventing hepatic fibrosis as a consequence. Also, having all segments in transit may be the reason that diarrhea has never been observed, except once in a case where the duodenal passage was shut. Worsening in the odor of feces or flatulence are rarely a complaint.

Eating without vomiting, no mechanical obstacles to ingestion of food, no diarrhea and no significant malabsorption provided these patients with an excellent quality of life.

Regarding the improvement in metabolic profile, nutrients reach distal small bowel in larger amounts

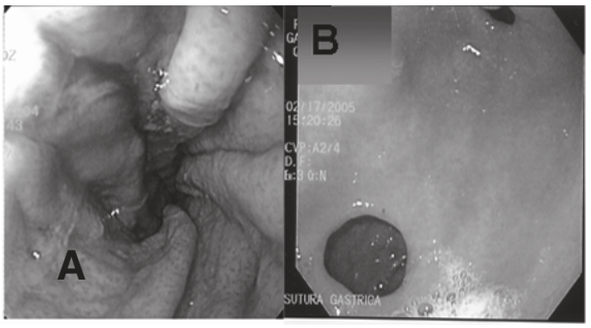

Figure 5. Endoscopic aspects. A – Sleeve gastrectomy. B – Pylorus (upper right corner) and gastroileo-anastomosis (lower left corner).

than they naturally would, stimulating nutrient detectors that intensify the secretion of GLP-1,[30] as shown here. Early and effective elevation of secretion of GLP-1 can cause a delay in digestive transit, central satiety, intense stimulus to trophism of pancreatic beta-cells and a strong insulin secretion to cure type II diabetes. Better secretion of PYY (and probably oxyntomodulin), also provoked by luminal nutrients, enhance satiety.

The operation also includes the resection of greater omentum, removing significant amounts of visceral fat which are clearly linked to metabolic syndrome. Visceral fat is an important source of plasminogen activator inhibitor 1 (PAI-1)[31] and resistin.[32] PAI-1, a substance that inhibits fibrinolysis, is related to cardiovascular risk. Resistin is an inductor of insulin resistance.

Lipolysis from visceral fat generates free fatty acids to the portal vein, which is related to hepatic

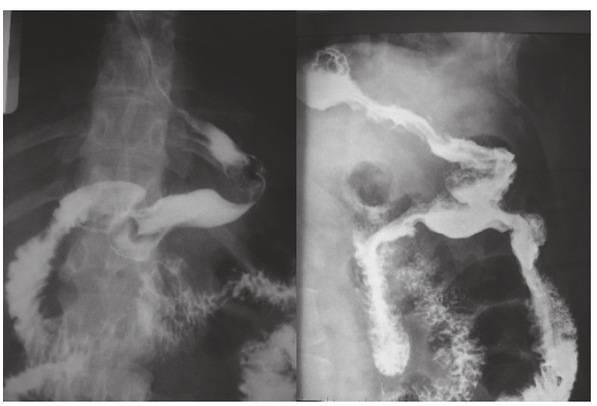

Figure 6. GI series. Frontal and profile views: contrast passes both ways.

insulin resistance, diminution in hepatic insulin clearance and hyperinsulinism. This favors the removal of visceral fat. Besides, systemic free fatty acids are related to a peripheral impairment of insulin action;[33] blood lipids and insulin resistance are related to an inhibition of nitric oxide production (a natural vasodilator) by vascular endothelium,[35] that also links visceral fat to type II diabetes and hypertension.

As a result of the sleeve gastrectomy, enterectomy and omentectomy, voluminous specimens are retrieved. This may result in reduction of the abdominal pressure, comfort, probably less gastroesophageal reflux and better venous return.

The proposed operation, at least in this first period of observation, provoked weight loss as efficiently as the most efficient bariatric procedures. Weight loss, better secretion of GLP-1 and PYY, visceral fat removal and less production of resistin ameliorate the diabetic status. Less food ingestion, less weight, less blood lipids, and normal blood glucose, all together help protect arteries, and the risk of atherothrombotic diseases probably falls intensively. As mentioned, there is a possibility that bringing more nutrients to the hindgut may also diminish the increasing incidence of colon cancer. Therefore, the proposed procedure, based on an innovative rationale, may be a contribution to help us face the most incident diseases of the modern world. The initial results of this new strategy are stimulating. Longer follow-up and a greater number of patients are needed.

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