

# Gut-Endocrine Axis - A Route for Diabetes Cure through Surgery?

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## ABSTRACT

In this review article, we explain the rationale for achieving remission of Diabetes Mellitus by surgical manipulation of the gut endocrine axis, and present the scientific evidence available thus far in support of the same. The evolution of 'metabolic' surgery is presented here. The reduction in mortality and co-morbidity is presented. The two main theories of causation of euglycemia are discussed in detail. Most authors now believe in both the theories, and the gastric bypass and the biliary pancreatic diversion are the procedures with the highest rate of remission. Finally, in the context of reappearance of hyperglycemia, the beneficial effects of a prolonged period of normal blood sugar are discussed.

Ever since the monumental article<sup>1</sup> in 1955, outlining the normalisation of sugar levels after gastrectomy, a causal link between gut surgery and correction of diabetes was suspected. However, it was also attributed to the weight loss suffered by gastric cancer patients or the liver metastases interfering with hepatic glycogenolysis. Subsequently, an epoch making article appeared in the annals of surgery (1995), documenting long term control for both obesity and diabetes with a gastric bypass. Authored by Walter Pories<sup>2</sup>, this paper analysed results based on 14 years of gastric bypass surgery and 608 patients.

This was a serendipitous finding in a cohort group that had the bypass but essentially as a weight reduction (bariatric) procedure. This was the first time that a direct link between gastric bypass surgery and blood sugar normalisation was established.

It was then believed by most surgeons and other researchers that the loss of weight, the reduction of caloric intake and the diminished insulin resistance accounted for these effects. However the last 20 years of research into gastrointestinal endocrine molecules has completely changed the direction of surgical logic.

Based on the varied metabolic effects of these procedures, the American Bariatric Surgery Society renamed itself as the American Society of Metabolic and Bariatric Surgeons (ASMBS).

Let us study the available procedures:

**1. Gastric Banding :** In this procedure a silastic or PVC band is inserted 2 to 3 cms below the OG junction, causing a functional obstruction of the upper gastric segment, and restriction of food intake. It is not a very effective form of Bariatric Surgery and seems to have very little metabolic component either. Although mild reductions of plasma glucose have been documented, its effects are more due to weight loss and resetting insulin resistance than due to a hormonal effect. Therefore there will be no more discussion about this procedure in this article.

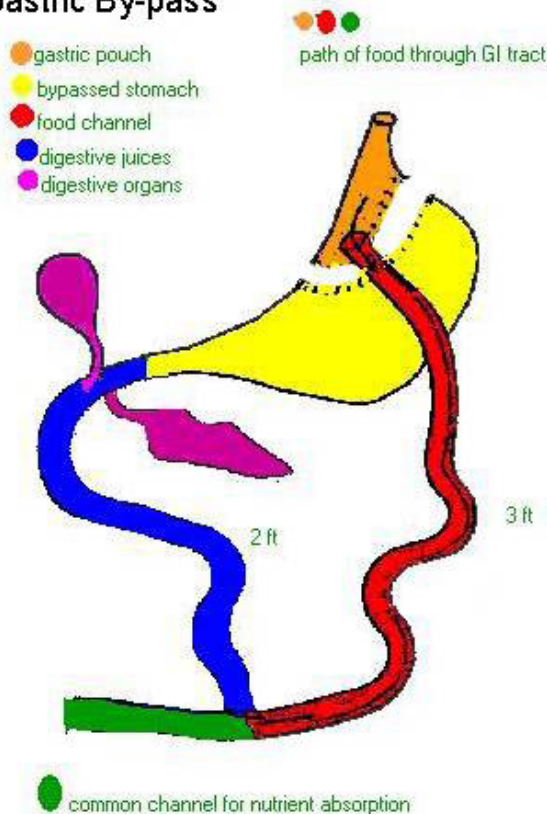
**2. Sleeve Gastrectomy:** In this increasingly popular procedure a sleeve is made of the stomach by resecting the greater curvature and three fourths of the left part of the stomach. This results in a maximal reduction of the gastric size, and also effects some endocrine changes by reducing serum levels of Ghrelin (*see Fig.*). Although this operation was initially thought to be merely restrictive, we now know that it has a prominent role in endocrine manipulation.

**3. Gastric Bypass:** In this operation the stomach is divided into a tiny proximal pouch and a large segment distally which is bypassed. The proximal jejunum is divided 50 cm from the duodenojejunal flexure and the distal limb is anastomosed to the stomach (*see fig.*). The proximal jejunum is now anastomosed to the distal jejunum 100 to 150 cm from the site of the GJ. This operation has been proved to be the most efficacious to restore euglycemia<sup>13</sup>.

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## Gastric By-pass



**4. Ileal transposition:** The newest of the procedures, interposing a considerable length of ileum within the proximal jejunum in an isoperistaltic manner, is a technique of incretin stimulation by the pathways described in greater detail later. The advantage of this operation is its use in lower BMI individuals, between 22-30 BMI. When used for higher BMI patients, a sleeve gastrectomy is added and the procedure is known as the SGIT (Sleeve Gastrectomy Ileal Transposition). However, compared to the sleeve and the bypass, this is still an experimental procedure.

## Bariatric and Metabolic Surgery

Although the procedures described for bariatric and metabolic surgery is the same, the latter term is used specifically for lower BMI individuals undergoing surgery for control of Diabetes, Dyslipidemias, Hypertension or any other component of the metabolic syndrome.

## Pathophysiology

Weight loss per se leads to reduction in blood sugar, a common finding in obese or overweight diabetics in the Indian subcontinent. Almost all diabetics undergoing metabolic surgery manifest normalisation of sugars within 2 to 3 weeks of surgery<sup>14</sup>, whereas weight loss takes several weeks or months to be achieved. There are two main pathophysiological theories put forth to explain the correction of diabetes in these patients. They are the foregut and the hindgut theories.

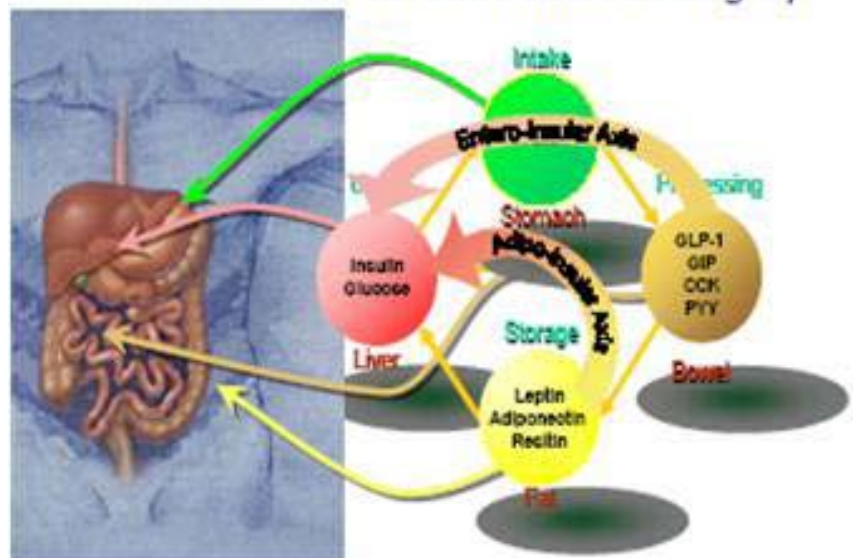
## Foregut Theory

This theory was first propounded by Rubino *et al*<sup>3</sup>. According to this group of workers the mucosa of the duodenum, coming in contact with the food releases glucagon which accounts for immediate post prandial hyperglycemia which is a consistent feature of the pre diabetic and diabetic state. A number of studies have shown that excess glucagon, rather than insufficient insulin is the major derangement in diabetes. Patients undergoing Roux en gastric bypass (RGBP) exhibit minimal or no increase in serum level of glucagon in the postprandial phase. The 'Rubino' factor refers to the putative duodenal contact cell which triggers off the glucagon release<sup>18</sup>.

## Recent Advances

Based on the Rubino hypothesis, the newest noninvasive treatment for diabetes mellitus is a loose and floppy plastic sleeve that completely coats the duodenum upto the jejunum, and introduced endoscopically. This is known as the Endo GI barrier and is said to be the treatment of choice in the future for low BMI patients with diabetes mellitus.

## Gut Hormones and Bariatric Surgery



**Hindgut Theory**

Proponents of the hindgut theory of diabetes control after RGBP invoke a set of internal insulin like secretions known as incretins. The latter are released from specialised cells of the ileal mucosa (K and L cells) which release a peptide known as GLP - 1. The latter is one of the most powerful insulin agonists known to man. It increases the serum insulin by whipping the beta cells of the pancreas. It is also anti apoptotic towards the beta cell, putatively prolonging their lifespan. Indeed there have been a few cases reported of Nesidioblastosis or idiopathic hypertrophy of the beta cells, which in post bypass cases is said to be mediated by GLP-1.

The other incretin that is released by the ileal cells as part of the "ileal braking mechanism" in response to early passage of semi digested chyme into the distal reaches of the ileum, is the peptide called GIP(Gastric Inhibitory Peptide).

PYY is another peptide that is released after gastric bypass<sup>16</sup>. Both GIP and PYY have anti glucagon effects, effectively tipping the balance in favour of insulin and pro-insulin molecules. Incretins are especially involved in the immediate post prandial glucose-insulin synergy. It is notable that high incretin levels in the post bypass patients correlate positively with lower post-prandial sugar levels<sup>17</sup>.

Most bariatric surgery protagonists subscribe to the combination of foregut and hindgut theories. What is beyond debate, however, is the rapid fall of blood sugars seen immediately after surgery.

**Time to Euglycemia**

Significant weight loss occurs about four weeks after bariatric surgery, about 8-10 kgs. The common statement of physicians, that improved glycemic control is a direct result of weight loss, cannot hold water as normalisation of sugars takes an average of about 2-3 weeks, when the weight loss is barely 4-6 kgs. This minimal loss of weight cannot account for complete euglycemia. It is now said to be a combination of two factors:

1. Incretin levels (*see Fig.*), especially GLP-1.
2. The sudden near total caloric restriction that occurs post operatively washes out the fat from the cytoplasm of the beta cells, in which fat accumulation prevents adequate and appropriate release of insulin. This is known as lipotoxicity, and lipid washout is putatively a cause for early normalisation of blood sugar.

**How effective are metabolic surgeries?**

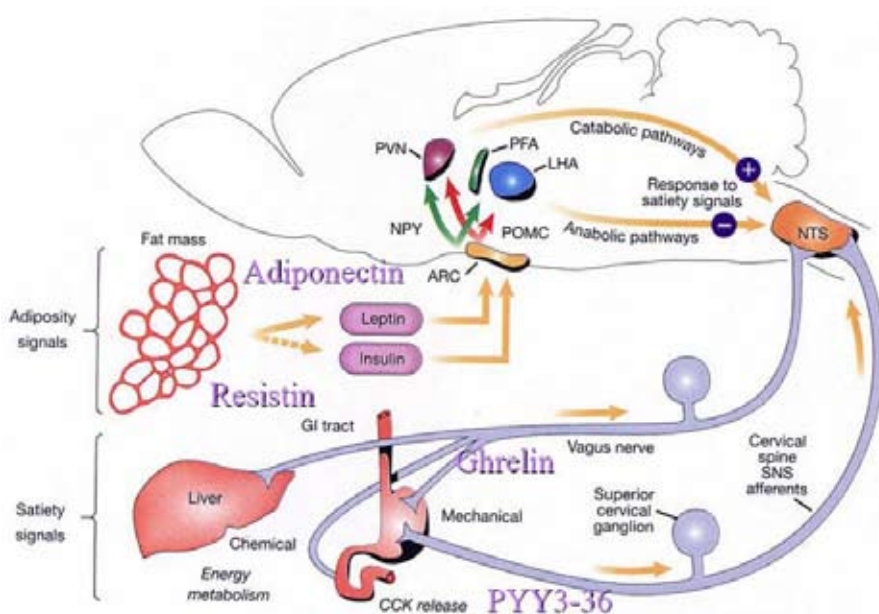
Looking at the data of Buchwald<sup>4, 11</sup>, Schauer<sup>5</sup>, Gagner<sup>6</sup> and Scopinaro<sup>7</sup>, several hundred thousand patients have been followed up in careful detail, and the average figures of diabetes remission (no drugs, no insulin) are 83% for gastric bypass, 67% for sleeve, and 48% for the band, in the Caucasian population. This figure approaches 95% for the biliopancreatic diversion of Scopinaro<sup>7</sup>. Our own experience over the last 11 years and that of several other Indian workers indicates a much higher percentage of remission in the Indian patient<sup>21</sup>. Perhaps insulin resistance which comes down sharply after bariatric surgery is an important factor, as is the viability of beta cells in our population<sup>19</sup>.

**'C' Peptide Evaluation**

In diabetics who are on insulin injections, the serum C peptide represents their indigenous insulin output, as all injected insulins have only the A and B peptides. Finding a serum C peptide of greater than 3 nanograms is a sign of a fairly well functioning pancreas with sufficient reserve to be stimulated by the incretins<sup>12</sup>.

**Other Comorbidities**

Diabetes is often one of a host of diseases, like dyslipidemia, gout, and hypertension. Several studies<sup>8,9,10</sup> have shown significant resolution of



these other ailments, to the tune of 80-90%. Also, like with diabetes, these parameters normalise very rapidly usually within a few weeks of the bariatric surgery<sup>20</sup>.

### Impact on Lifespan

The WHO figures and the Framingham study<sup>24</sup>, 15 figures indicate that an obese smoker loses about 13 years of his life, and an obese non-smoker about 10. Definite evidence has accumulated that these operations significantly increase the life span of the patient. Death due to vasculopathy of the coronary and cerebral vessels is especially prevented by this surgery. Also, the fluctuating insulin levels seen in poorly controlled diabetes trigger instability of the DNA, and trigger off the neoplastic process. Reversal of the diabetic state decreases the risk of cancer occurrence in this group of patients.

### Small Vessel Disease

Diabetic retinopathy and nephropathy occur in up to 38% of patients who have well controlled sugars<sup>18</sup>. The disease process seems more related to the duration of the diabetes. Effecting a reversal of diabetes in these patients will move them to a 0% risk group as in the non diabetics. This is a very powerful reason for attempting reversal of diabetes through surgical procedures<sup>23</sup>.

### How long do they last?

A recent slew of articles has indicated that 5-10% of patients who undergo metabolic surgery return to the diabetic stage when followed up for 10-15 years. The medical community was quick to denounce these operations as merely temporary successes. However, careful follow up data now indicates that even in this small percentage of patients who relapse into the hyperglycaemic state, the arteriolar disease when followed up longitudinally, is much less than their non operated counterparts. Thus, the current understanding is that a period of euglycemia of 10-15 years is remembered by the cells with a much better vascular prognosis in this group of patients. This phenomenon is called "metabolic memory" of the cell, and is evoked to explain the overall better prognosis.

### Conclusion

The last word about metabolic surgery has not been spoken, and will not be spoken for a long time. What emerges from a vast amount of data is that there is definitely seems to be a role for attempting to reverse the diabetic process, and that doing so positively impacts upon the health and longevity of the individual. Until futuristic magic pills arrive upon the scene, the most efficacious treatment available right now is metabolic surgery.

For the higher BMI individual (32 and above), the Roux-en-Y gastric bypass remains the best option. In lower BMI individuals, the ileal transposition is an attractive alternative. Definite slowing down or reversal of microangiopathy has been documented in patients undergoing these operations. Incretin release either through the foregut or hindgut theory seems to explain return to euglycemia, which occurs within a few weeks of the procedure. Metabolic memory of the cell gives a survival and morbidity advantage, even in the small percentage of metabolic surgery patients who return to a hyperglycaemic state, thus indicating this procedure<sup>22</sup>.

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