Ileal Interposition - For Type-2 Diabetes

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HISTORY:

Historically it has been recorded that following some gastro-intestinal bypass operations of the patients got relived of their diabetes. Since bariatric surgery started many years ago. Some of those obese patients who were also diabetic dropped their sugars levels soon postoperatively and a twenty year follow up has shown them to be still under control. Bariatric surgery can control T2DM to varying extents (40%-98%) in morbid obese patient. The pathophysiologic mechanisms where by bariatric surgery reaches the described results are not yet well understood. Rubino and Gagner Maintained that the presence of an intestinal factor derived from excessive stimulus of the upper digestive tract causes a deficient incretin action. Improvement or resolution of T2DM by gastric bypass operations much before any effective weight loss is consistent with a hormonal mechanism.

Naslund reported high level of incretin GLP-1 in patients 20years after jejuno-ileal bypass, suggesting that T2DM may be adequately controlled by GLP-1 in the long term. Mason finally proposed that the ileal interposition producer may be the ideal operation for treatment of T2DM.

Dr.Aureo De Paula of Brazil did research on this phenomenon and then tested his results in the lab on rats, to prove the GLP-1 hormone increase is responsible for lowering of blood sugar following ileal interposition.

Thus, he could put forward a surgery which was inclusive for control of diabetes and thus useful for non-obese individual also. He has already done more than 600 ileal interposition in last 7 years.

DIABETES

T2DM is a chronic metabolic disease effecting about 285 million people worldwide. The disease is associated with significant morbidity through its micro vascular complications, which causes blindness secondary to retinopathy, kidney failure due to nephropathy and amputations due to
neuropathy. Ultimately, a majority of patients with diabetes die from the macro-vascular complications of premature atherosclerosis.

Two major pathophysiologic abnormalities underlie this complex disease: increased resistance to insulin action at the level of the liver, skeleton muscles, adipose tissue, and progressive qualitative and quantitative decline in pancreatic cells function.

It is postulated that the pathologic sequence of events leading to T2DM is characterized by failure of beta cells to secret e adequate amounts of insulin to compensate for insulin resistance in peripheral tissue and by increased endogenous glucose production. The deterioration of secretion and insulin action is present for many years before the diagnosis of diabetes.

However for non-obese T2DM, insulin resistance is not essential to development of diabetes, applying an essential role for impaired insulin secretion. This operation is effective in T2DM.

In T1 DM , no beta cells are present which can be stimulated. Thus this operation can only be done in T2DM with enough beta cells reserve.

INCRETIN EFFECT AND INSULIN SECRETION

It has been seen that if the same amount of glucose in given intravenously and orally, the serum insulin level rises more when glucose is ingested compare to intravenous injection. This phenomenon is called incretin effect. This effect is due to release of some gut hormones when undigested food comes in contact with gut. Although more than 200 incretins have been identified there are two major gut hormones which are responsible for the most of the insulin increase in a normal person. They are GIP (gastric inhibitor peptide) and GLP-1(Glucogon like peptide).In T2DM, their incretin effects are either greatly impaired or absent.

GIP is a peptide secreted by the duodenal K-cells in response to ingested fat and carbohydrates. In obese T2DM patients, its receptor on beta-cell is down-regulated.GLP-1 is a peptide secreted by the gut L-cells mainly in distal ileum, and in T2DM, its secretion is impaired.

Modification of the enteroinsular axis (which is impaired in T2DM patients) can give long-term control of T2DM by ensuring durable GLP- delivery, both during fasting and after meal ingestion, induces L-cell stimulation by early arrival of nutrients in the distal ileum. The secretion of GLP-1 influences glucose metabolism by inhibiting glucagon secretion, stimulating insulin secretion, delaying gastric emptying and stimulating glycogenogenesis.
Evidence of increased GPL-1 secretion and improved glucose tolerance, was also proven by the fact that, this effect was reversed by GLP-1 receptor antagonism.

In a normal person there are two phases of insulin secretion following ingestion of food to bring blood sugars under control. The early phase plasma insulin response comes within 0-20 minutes after ingestion of food, when food reaches upper part of jejunum. This is maximally due to release of gut hormone GIP. This hormone is the main hormone for increase of insulin and thus controlling blood sugar. There is a second phase of insulin increase when food reaches distal ileum and GLP-1 is secreted. This phase comes after 20 minutes to 2 hour of ingestion of food. The peak secretion of insulin is small at this because the intestinal stimulation is less as food is already digested and hence only generates a weak stimulus.

In T2DM the GIP hormone is produced but is not effective in increasing the insulin secretion. Thus the person becomes a diabetic but the mechanism of GLP-1 is still maintained. This GLP-1 secretion even though normal, is not enough to control his diabetes, as it is too weak to stimulus and comes too late after ingestion of food.

**MEDICATION IN T2DM**

Many of the currently available antidiabetes agents address the twin abnormalities, but their use is often limited by an adverse side effect profile that includes hypoglycemia (insulin sulfonylureas and glinides); weight gain insulin (thiazolidiones(TZDs),insulin,sulfonylureas and glinides); and edema(TZDs). Perhaps most importantly, today most of the therapeutic agents do not definitively preserved and promotes pancreatic cell function.

Clinical studies show that both Exenatide (the first dipeptiyl peptidase-4-resistant glucagoan, peptide-1 receptor agonist approved by the Food and Drug Administration (FDA)), and liraglutide (a long –acting incretin mimetic), improves beta cell function and glycemia with minimal hypoglycemia. Both agents have trophic effects on beta-cell mass in animal studies. The use of these agents is also associated with reduce body weight and improvement in blood pressure, diabetic dyslipidemia, hepatic function of myocardial function. These effects have been potential to reduce the burden of cardiovascular disease, which is a major cause of mortality in patients with diabetes.

The mode of action appears to be a reduction in pancreatic apoptosis, an increase in beta-cell proliferation or both. Thus, the effects of GLP-1 receptor stimulation are not based on insulin replacement but apparent repair of the pancreas. Similar data suggest that the same effect may
occur in other peripheral tissues. More, recently the role of GLP-1 has been studied in nervous tissue. As in the periphery, it appears to promote cellular growth and reduce apoptosis. In models of Alzheimer’s disease, Parkinson’s disease and peripheral neuropathy, stimulation of the GLP-1 receptor has proved to be highly beneficial.

Despite adequate drug therapy with antidiabetic medication, glucose and HbA1c measurements steadily increase with time, reflecting the ongoing deterioration of beta cells.

METABOLIC SURGERY

A recent systematic analysis of 621 studies in the English literature including over 135,000 morbidly obese patients undergoing bariatric surgery, reported resolution of T2DM (defined as discontinuation of all diabetes-related medications and blood glucose levels within the normal range) in 78% of cases.

Furthermore, in a retrospective cohort of 7,925 bariatric patients, deaths attributed to diabetes were reduced by remarkable 92%.

Finally in 85,000 morbidly obese patients, early (3-30 days) and late (>30 days to 2 years) mortality rate for bariatric surgery have trended downward (0.28% and 0.35% respectively.)
Thus, in the every obese patient with T2DM (i.e. with body mass index (BMI) >_3d 35kg/m2), bariatric surgery appears to be a treatment modality that is both highly effective and increasingly attractive. Apart from controlling blood glucose levels it also has beneficial effect on other aspects of body function. Triglyceridemia is controlled, HDL shows an increase. Blood pressure gets controlled. Microalbuminuria comes within normal limits. If patient is obese, a sleeve gastrectomy reduces excess weight. GLP-1 helps in reducing weight and at the same time preserving lean body mass.

ADVANTAGES OF ILEAL INTERPOSITION

This operation will re-regulate the body’s own mechanism in such a way that more insulin is produced in the body every time one has food so as to mimic the normal pattern of insulin secretion. This is achieved by taking the help of incretin effect (GLP-1 hormone) from the ileum which is still active in T2DM. This give good long-term control of diabetes with a better quality of life than other procedures.
**BASIC MECHANISM OF ILEAL INTERPOSITION**

A long segment of ileum is interposed between duodenum and jejunum. Thus undigested food enters first into interposed ileum which strongly stimulates and increases the secretion of GLP-1 from this gut. The stimulation now comes within 10 minutes of ingestion of food as in normal person. These repeated food stimulus gradually increase GLP-1 secretion and hence increased insulin levels. In a period of few weeks to 3 months patient starts going off all medication.

Initially, the role of the bypass of foregut was considered important because bariatric operation like the gastric bypass, bypass K-cells in the duodenum responsible for secreting GIP. The lower level of GILP causes up regulating of GIP receptors of beta cells and improvement in insulin resistance. Other researchers have questioned the role of the bypass of foregut as the mechanism of diabetes control. Jejunoileal bypass(JIB) resolves T2DM but does not bypass the upper GIT. Moreover, in animal models, ileal interposition, a procedure in which a small segment of the distal ileum has been transposed proximally has led to similar results. This has led to a greater interest in the premature exposure of ingested nutrients to the distal ileum which determines a series of events, among which are an increase in GLP-1 and motor alterations in the upper gastrointestinal tract, called the “ileal brake”

This early presentation of chyme to ileum leads to stimulation of L - cells and an increased secretion of Glucagon like petide-1 (GLP-1). This peptide has a potent glucose dependent action on the beta cells of pancreas. This results in increased insulin secretion and improvement of Diabetes. In the stomach GLP-1 has an inhibitory effect on gastric motility thus delaying the gastric emptying. This may also contribute to the improvement of diabetes, as less insulin will be required due to slower availability of food in the intestines.

The “ileal brake” describes the decrease in the contractions of the gastric antrum and a delay in the emptying of the stomach, as well as a decrease in the duodenal and jejunal motility.

This operation may be an ideal operation for surgical cure of diabetes in non-morbidly obese patients also, as there is no malabsorptive element leading to the weight loss.

The gastric restrictive element of the bariatric operation has no role in glycemic control in this model. This has been elegantly demonstrated by Rubino et al in their study on non-obese diabetic rats where a gastrojejunal bypass (GLB) was done with an intact gastric volume. There was a marked improvement in the fasting plasma glucose levels in all the rats that underwent GLB. However, it will contribute to some weight loss.

Despite the significant link between obesity and T2DM, 20% of patients with T2DM are not obese and some of these patients are unable to achieve adequate control of their blood glucose despite dietary and pharmacological treatment. In these non-obese patients, DM 2 is still
associated with significant morbidity such as blindness, renal insufficiency, neuropathies, amputations, and cardiovascular disease and reduced life expectancy. While a significant body of research exists showing that bariatric surgery can reverse T2DM in obese individuals, there is limited but promising evidence of its efficacy in the non-morbidly obese population. In T2DM patients with normal BMI, conventional bariatric surgery would be inappropriate, as it would lead to significant undesirable weight loss. In such patients ileal transposition may be the future.

**PATIENT SELECTION**

1. Ensure patient has T2DM – GAD Antibody test / IAA test / History of control with drugs for 5 yrs; very important to exclude LADA (Latent Auto-immune Diabetes of Adults) as these pts are T2DM in disguise as Type – 2

2. Duration of Diabetes = 3-15 yrs (better results) (though complete resolution obtained even with 25 yr old DM)

3. C-peptide fasting > 1 ng/ml (higher is better) = indication of B-cell reserve; C-peptide 1 hour after meal to check the meal – stimulated response, assessing B-cell response.

4. Age = 18-70 yrs; activity & fitness are important.

**PROCEDURE**

The operation is done by Laparoscopy using 6 ports & staplers are used for anastomosis. There are three transections & three anastomoses in the small intestine. A 1.5 – 1.7 meter segment of distal ileum is prepared along with its mesentery & is interposed and anastomosed to jejunum, side to side, just after the duodeno-jejunal junction. The distal part of jejunum is anastomosed to distal part of interposed ileum. Ileo-ileal anastomosis completes the procedure. Thus there is no shortening of intestine length.

The fundus of stomach is excised to remove another gut hormone called Ghrelin, also called the ‘hunger hormone’ Ghrelin secretion reduces insulin activity. Thus ghrelin hormone removal increases insulin activity & adds to the effect of ileal interposition.

A variation of this ‘Standard Ileal interposition’, is the ‘Diverted ileal interposition; here the 1st part of duodenum is transected and the proximal end of Ileal segment is anastomosed to the proximal duodeno – gastric end. The distal end of ileal segment gets a side-side ileo-jejunal anastomosis about 50 cms distal to the Ligament of Treitz, with a diversion of the duodenum.
and proximal jejunum. This is done in some patients, who have a very chronic disease, are ‘slim diabetics’ have low C – peptides and insulin resistance and severe dyslipidemia.

This improves the incretin effect to a great extent, as there is no more anti – incretin activity by the ‘duodenal or Rubino factor’ which gets stimulated when food passes through and in contact with, the duodenal and proximal jejuna mucosa.

RESULTS

Indicators of Success

- Diabetes is said to be resolved when Hb1c <6%, FBS< 100mg%, without drugs. LDL <100 mg / dl, and triglyceride < 150mg / dl
- Achieved in 91% after 5 years and none of the operated patients required insulin
- Hormonal results after 1 ½ yrs
- GLP – 1 increased at fasting, 30 min and 60 min = 8.78+/− 9.3 to 11.5 +/-2.42ng / ml
- Metabolic Benefits
- 86.7% of patients achieved adequate glycemic control (HBA 1c <7%)
- HBA1c < 6% was achieved by 69.7% after a mean follow-up of 7.4 months.
- Hyperinsulinemia reduced in all patients.
- Hypertriglyceridemia normalized in 81.7%; HDL> 40 in men & > 50 in women in 90.3%
- Hypertension came under control in 90.5%=(130/86)
- Macroalbuminuria got resolved; Microalbuminuria resolved in 86.7%
- All patients with reduced GFR (60-89), normalized >90ml / min
- 30% showed objective improvement in retinopathy Central obesity resolved in all patients – men<102cm, women <88cm
- Neither baseline weight nor weight loss was a significant predictor of remission, nor were sex, age, severity or diabetes duration. The only parameter predicting diabetes resolution, was a lower baseline insulin sensitivity.
- In addition to weight loss, ileal interposition with sleeve gastrectomy impacts on T2DM by a direct mechanism, principally involving restoration of insulin sensitivity [4]

OUR RESULTS

In a study conducted by us we have done 32 cases since the first case done on 18th Feb 2008.

We enrolled T2DM with any BMI. All were T2DM with inappropriate glycemic control despite dietetic, oral hypoglycemic therapy and or insulin. Patients underwent ileal interposition in the
proximal jejunum and a sleeve gastrectomy, the size of sleeve gastrectomy depended on patient’s BMI.

The results of first ten cases (four men, six women) were published (Diabetes Technology & Therapeutics ....volume 11’ Number 12, 2009...mary Ann Liebert, Inc.). All patients had diabetes for more than 3 years with poor control despite use of oral hypoglycemic agents (OHAs) and/or insulin. The primary outcome was remission of diabetes (hemoglobin A1c<7% without OHAs/insulin), and secondary outcomes were change in OHA requirement, components of metabolic syndrome, insulin resistance and microalbuminuria. Results; We reported the preliminary postoperative follow-up data of 9.1 +/-5.3 month (range,2-16 months). Participants had a mean age of 48.2+/- 9 years (range, 34-62 years)(range 4-25 years), and preoperative body mass index of 33.8+/-6.5 kg/m2. Seven patients had diabetes remission, and the remaining three showed significantly decreased OHA requirement. All participants had weight loss range between 15% and 30% and had remission of hypertension. Microalbuminuria (96.8+/-19.1 vs. 46.7+/-10.1 mg/L, P ¼ 0.03568) and insulin resistance as assessed by homeostasis assessment model of insulin resistance (5.2+/-2.1 vs. 1.8+/-0.9 P ¼ 0.0005) decreased significantly after surgery.

At present, resolution of T2DM is complete in 13 out of 32pts. With a marked reduction of OHA requirement in the rest; all who required insulin have stopped it. Significant weight loss (when required) has been achieved; glycemic improvement, independent and disproportionate to weight loss has been seen and there is no evidence of malabsorption / nutritional deficiency.

Sex (M-18/F-14); age (29 -62 yr); Duration of DM (3-25yr)

Pre op. diabetes Rx=23 / 32 insulin + OHA; 9 – OHA only

Hypertension 22 / 32 (All under control)

No blood transfusions have been needed for surgery.

Post – operative = No significant complications so far; pts have burping, reflux, minimal dysphagia, weakness for a few days, which settle down very soon.

Blood pressure, glucose levels and urine outputs are checked and kept in the normal ranges; the drug requirements are reduced as the incretin responses improve. [5]

**Nutritional / Malabsorption issues & Quality of Life**

Patients have been followed up with serum Vitamin b 12 & Se. Iron studies upto two years. None has decreased in post operative period, showing that there is no malabsorption. Likewise
there is no disturbance in the absorption of other minerals and vitamins. It is postulated that jejunalization of interposed ileum occurs in the long run with the digestive function and mucosa, while the endocrine function of secreting GLP-1 remains intact.

**LONGTERM EFFECT**

It has been proved conclusively in rats and in-vitro studies that persistent increase of GLP-1 for 3-4 years causes an increase in number of beta cells in pancreas.

In GK rats, ileal interposition significantly improved glucose tolerance, insulin sensitivity, and acute insulin response without affecting body weight and food intake. Immunohistochemistry revealed remodeled islets strictly resembling that of euglycemic rats and signs of beta cell neogenesis staring with exocrine structures. Gene expression of proglucagon, Proconvertase 1/3(PC1/3), and chromogranin A in the transposed ileum is significantly enhanced.

Thus the ultimate control of diabetes is expected to be assured in long term.

**CONCLUSION**

Bariatric surgery currently is considered to be the most effective long term treatment of human obesity and often leads to remarkable improvement in diabetes. Reduction of blood sugar which indicate reversal of T2DM is due to exclusive changes in hormones produced by gastrointestinal tract may contribute to the early effect of bariatric surgery in addition to later effects of weight loss.

Ileal interposition increases GLP-1 and peptide XY levels possibly because of early stimulation of distal small bowel with relatively undigested nutrients .This improves insulin secretion and possible action.