

## DRUGS OR SURGERY? FOR CONTROL OF TYPE-2 DIABETES MELLITUS

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Type 2 diabetes is one of the fastest growing epidemics in human history and is usually related to obesity [1]. The condition is not very uncommon in non obese person [2]. Tight glycemic control with medication (HbA1c less than 7%) has been shown to decrease the risk of micro vascular complications like retinopathy, nephropathy, and neuropathy, associated with diabetes in 2 large randomized studies (United Kingdom prospective diabetes study, UKPDS, and diabetes control and complications trial, DCCT) [3,4].

Both studies showed that for drop of 1% (ie, from 9% to 8%) HbA1c there was a relative risk reduction of 25% to 45%. Glycemic control to achieve a HbA1c 7% in some of these patients was only possible with insulin doses > than 100 units per day and even then for only short periods of time [3]. It is believed that in community settings where >95% of diabetic patients are treated, that HbA1c levels in T2DM patients typically vary from 8.5 to 9% suggesting that tight control with medication is difficult to achieve [3]. Furthermore, intensive medical therapy required to achieve a HbA1c  $\leq$  7% has a corresponding 2%-4% yearly incidence of severe hypoglycemia and often death.

So we need persistent glycemic control but method must be safer. "And so it is. Just as Walter Pories said, we surgeons were unprepared to adequately assess the observation that gastric bypass surgery cured type 2 diabetes mellitus (IIDM)". The scenario was observed by Friedman MN.et.al in the year 1955 in patients that underwent subtotal gastrectomies [5]. But the message not only draws attention, also initiates debate among endocrinologist, surgeons and physicians. It was again observed in 1982 after remission of diabetes for the first time following a gastric bypass [6]. However, its practical importance was never valued until introduction of bariatric surgery, in which surgery done to reduce body weight.

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After a 16-year study comparing two cohorts that had similar original characteristics (one that underwent bypass surgery and one that refused surgery), the remission rate of T2DM for the surgery group was confirmed at 83%, with improvement in complications, and a reduced mortality from 4.5% to 1% ( $P < .0001$ ) [7].

So it should be the curiosity, what surgery, how surgery can improve or cure T2DM. Who is the appropriate candidates? Is it possible to do it in our country? Is it without any side effect? Is the improvement or cure permanent?

Currently available antidiabetic surgery are: some sorts of gastro duodenal Roux-en Y bypass, biliary pancreatic bypass, gastric resection or ileal transposition. In Roux-en Y gastric bypass (most accepted method) stomach is anastomosed to jejunum.

It is the incretin and anti incretin those were involved in improvement of diabetes after surgery. Anti incretins like dipeptidyl peptidase-4 (DPP-4) is responsible for insulin resistant, secreted from duodenum in response to food. Secretion of DPP-4 is reduced if duodenum is bypassed or food passes very rapidly (as in sleeve gastrectomy). On the other hand incretins like GLP-1 (Glucagon like peptide) and GIP (glucose-dependent insulinotropic polypeptide) are proinsuline, increase insulin released from the beta cells of the islets of Langerhans after eating, before blood glucose levels become elevated. They also slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake. It is the foregut hypothesis by Rubino [7].

The hindgut theory by Cummings et al proposes that the rapid transit of nutrients from the stomach to the hindgut as in Roux-en Y gastric bypass, cause more secretion of GLP-1 from L cell of intestine which is insulin analogue, stimulates  $\beta$  cell to secrete more insulin [8]. In addition in ileal transposition there is more stay of food in the ileum cause ileal hypertrophy, utilizes and retain more glucose after food intake, responsible for slow absorption of glucose. The two theories are not mutually exclusive.

Right now the surgery done in diabetes with BMI >35 is associated with some sorts of reduced absorption of nutrients. What will be in case of uncontrolled non obese diabetics? Animal study on non obese subjects is going on. Study shows that ileal transposition is the method of choice in non obese subjects [9]. In this method there is delay in food passage in the ileum, causes more secretion of GLP-1 and transient glucose entrapment in the ileum.

In terms of duration and sustainability, recent retrospective analysis shows clinical outcomes of 217 patients with T2DM who underwent bariatric surgery between 2004 and 2007 and had at least 5-year follow-up. Complete remission was defined as glycated hemoglobin (A1C) less than 6% and fasting blood glucose (FBG) less than 100 mg/dL off diabetic medications. Changes in other metabolic comorbidities, including hypertension, dyslipidemia, and diabetic nephropathy, were assessed.

In one study at a median follow-up of 6 years (range: 5–9) after surgery (Roux-en-Y gastric bypass, n = 162; gastric banding, n = 32; sleeve gastrectomy, n = 23), a mean excess weight loss (EWL) of 55% was associated with mean reductions in Hb A1C from  $7.5\% \pm 1.5\%$  to  $6.5\% \pm 1.2\%$  ( $P < 0.001$ ) and FBG from  $155.9 \pm 59.5$  mg/dL to  $114.8 \pm 40.2$  mg/dL ( $P < 0.001$ ). Clinical outcomes of 217 patients with T2DM who underwent bariatric surgery between 2004 and 2007 and had at least 5-year follow-up were assessed which showed Hb A1C less than 6% and fasting blood glucose (FBG) less than 100 mg/dL off diabetic medications [10]. So we can consider it is persistent.

The surgery is applicable in our setting and probably in non obese diabetic particularly in uncontrolled diabetes in the form of ileal transposition.

We can hopefully expect to start the surgery without any delay.

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