Diabetes is predominantly an intestinal disease

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**ABSTRACT**

Diabetes mellitus (DM) is a chronic, progressive, medically incurable disease and is poorly controlled in a vast majority, in spite of tremendous advancements in pharmacotherapy. Altered gut microbiome can predict diabetes. There is strong and consistent evidence regarding role of the gut and many gut hormones like incretins in energy and glucose homeostasis. Incretin group of agents including glucagon-like peptide (GLP-1) receptor agonists and dipeptidyl peptidase IV (DPP-IV) inhibitors are efficacious therapeutic agents in diabetes treatment. A growing body of evidence, however, appears to indicate that type 2 DM (T2DM) may be an operable intestinal illness—a novel revolutionary concept about an old disease. This may facilitate research that can better clarify our understanding of the etiology of the disease and provide a new opportunity to develop new and more effective therapies. Future research should focus on an approach to bypass the bypass, that is, to replace the gastric bypass by equally effective but less invasive treatments for majority of diabetics.

Key words: Bariatric surgery, gut microbiota, type 2 diabetes, gastric inhibitory polypeptide, GLP-1

**INTRODUCTION**

Diabetes mellitus (DM) is a chronic disease with increasing worldwide prevalence. Type 2 DM (T2DM) accounts for majority (90-95%) of diabetes and is a growing epidemic that poses a huge burden on healthcare systems, especially in developing countries. T2DM is a progressive disease, its etiology is still elusive and conventional therapies cannot achieve a cure.

The current epidemic growth of diabetes, demands novel approaches for better understanding and treatment of this disease. We try to explore the evidence in support of the hypothesis that T2DM may be a disease characterized by a component of intestinal dysfunction.

The connection between gut microbiota and energy homeostasis and low-grade inflammation contribute to dysregulation of normal glucose tolerance. In animals models, altered gut microbiota led to development of obesity, insulin resistance, and diabetes by altered fatty acid metabolism in adipose tissue and liver, modulation of gut peptide YY and glucagon-like peptide (GLP)-1 secretion, activation of the lipopolysaccharide toll-like receptor-4 axis, and modulation of intestinal barrier integrity by GLP-2.

Gut bacteria were recently proposed to contribute to differences in body weight, insulin sensitivity, glucose metabolism, and other cardiometabolic risk. A recent study by Karlsson et al., found that the gut microbiome with abundance of particular bacterial species in the gut could differentiate diabetic vs normal glucose tolerant individuals with a degree of accuracy similar to that of traditional predictive models. The bacterial species most predictive of T2D was not consistent across different ethnic groups.

In mice with substantial changes in their gut microbiome were unable to make fatty acid synthase (FAS) in the intestine developed chronic inflammation in the gut, a powerful predictor of diabetes. People with diabetes also have defects in FAS.

The gut is the most exciting endocrine organ in the body with important neuroendocrine role of the gut in energy homeostasis, a finding consistent with evidence that many gut hormones are involved in glucose homeostasis. Incretins are hormones released from the gut into the
bloodstream in response to ingestion of nutrients in the food, and modulate the insulin and glucagon secretory response to food. The incretin effect accounts for at least 50% of the total insulin secreted after oral glucose.Incretin hormones are insulinotropic, that is, they induce insulin secretion at usual physiological concentrations seen in the plasma after food ingestion.[9]

The two major incretins in humans are GLP-1 and gastric inhibitory polypeptide (GIP) and share a considerable amino acid identity. They both increase insulin secretion; however, only GLP-1 suppresses glucagon secretion. Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV).[5] Endogenous GIP is a 42-chain amino acid peptide secreted by the lymphocyte K cells, in proximal duodenum and jejunum. The primary action of GIP is to stimulate glucose-dependent insulin secretion, but GIP also promotes proliferation of β cells and its survival.[9] Hyperglycemia downregulates GIP receptor expression reducing β cell response to GIP. Thus, enhancement of GIP signaling may have beneficial effects in patients with T2DM, but these benefits remain to be determined in clinical practice.

Endogenous GLP-1 is a gastrointestinal (GI) hormone secreted from the L cells of the distal aspect of the small intestine. Like GIP, GLP-1 achieves its insulinotropic effects by binding to its specific receptor (GLP-1R) that is positively coupled to increases in intracellular cAMP and calcium levels in β cells. In addition to its insulinoctrpic effects, it inhibits gastric emptying, decreases food intake, inhibits glucagon secretion, and slows the rate of endogenous glucose production; all of which help to lower blood glucose in T2DM. It has also been shown to protect β cells from apoptosis and to stimulate β cell proliferation by upregulation of the β cell transcription factor, pancreatic duodenal homeobox-1 protein (PDX-1), which is known to augment insulin gene transcription and upregulate glucokinase and glucose transporter 2 (GLUT2). Continuous GLP-1 treatment in T2DM can normalize blood glucose, improve β cell function, and restore first phase insulin secretion.

Both GLP-1 and GIP are proteins that are rapidly degraded by DPP-IV. These peptidases are ubiquitous serine proteases that are widely distributed in numerous tissues. By cleaving N-terminal amino acids, they cause inactivation of both GLP-1 and GIP. The DPP-IV inactivation process results in greater than 50% inactivation of GLP-1 within 1–2 min, and greater than 50% inactivation of GIP within 7 min.[9] An impaired incretin effect occurs in patients with T2DM in response to both oral and intravenous administration of glucose. Regardless of the method of glucose administration, the insulin response is delayed, blunted, and prolonged in patients with T2DM; compared to that in healthy subjects. The incretin effect may have important implications in reducing meal time hyperglycemia in individuals with T2DM. Data from published clinical trials using long-acting GLP-1 receptor agonists (liraglutide, exenatide long-acting release (LAR), albiglutide, taspoglutide, Lixymia) reveal significant reductions in HbA1C with greater reductions in HbA1C with liraglutide compared with the DPP-IV inhibitor.[7] Results with exenatide LAR demonstrated that these improvements in HbA1C could be maintained after 2 years.[7]

The anatomical rearrangements of the GI tract cause changes in energy and glucose homeostasis and that it in turn influences diabetes. Diabetes rapidly resolves following Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD). A meta-analysis of 136 studies with 22,094 patients demonstrated that T2DM resolved completely in 76.8% and resolved or improved in 86.0% of patients who had undergone bariatric surgery.[8] Complete remission of diabetes occurs in 48% of patients after laparoscopic gastric banding, 84% after RYGB, and 95% after BPD. Diabetes remission after RYGB and BPD is also durable, and recurrence of diabetes 10 years after surgery is rare. RYGB and BPD can cause complete remission of diabetes in days to weeks, long before substantial weight loss; whereas diabetes remission after laparoscopic gastric banding typically occurs over weeks to months, consistent with weight loss.[8]

Two hypotheses have been proposed to explain which part of the typical anatomical rearrangement of RYGB is essential for the effect on diabetes.[8] The hypothesis of the distal bowel suggests that excluding the duodenum and proximal jejunum results in expedited delivery of the chyme into the distal intestine, enhancing the release of GLP-1 and other gut peptides like peptide YY (PYY); which improve insulin secretion and action. The alternative hypothesis of proximal intestine is that the exclusion of the duodenum and proximal jejunum from the transit of nutrients may prevent secretion of a putative signal that promotes insulin resistance and T2DM. To explain how duodenal exclusion improves diabetes and possible contribution of proximal small bowel to pathophysiology of diabetes, Rubino developed anti-incretin theory.[10] The incretin system can lead to hypoglycemia, it is reasonable to consider a counterregulatory “anti-incretin” system having opposite actions preventing hypoglycemia. A balanced between incretins and anti-incretin (s) is necessary for normoglycemia, a shift toward excess anti-incretin would cause T2DM by impaired insulin secretion and sensitivity. Currently there are no candidates for the anti-incretin
role. However, that GIP action and the expression of its receptor are defective in diabetics and early phase insulin secretion, which is regulated by GIP, is blunted in people with T2DM. These abnormalities are consistent with a potential proximal anti-incretin factor interfering with the GIP system. The reversal of the alteration of the early phase of insulin secretion after RYGB35 suggests a possible return to normal GIP functions. Further research in this direction is necessary.

Recent experimental studies have suggested the rearrangement of GI anatomy as a primary mediator of the surgical control of diabetes. A study in diabetic Goto-Kakizaki (GK) rats that supports the proximal hypothesis, showed that enhancing delivery of nutrients to the hindgut without excluding nutrient flow through the proximal intestine (via a simple gastrojejunostomy (GJ)) does not improve diabetes.[9] But duodenal-jejunal bypass (DJB), with similar shortcuts of nutrients as in GJ, also includes the exclusion of the proximal intestine from the flow of nutrients, improved glucose tolerance, and fasting glycaemia.[9] Glucose intolerance returned when DJB was reversed, even though the GJ was preserved. This experiments shows that the exclusion of the duodenum is critical for the effect on diabetes. However, preventing duodenal passage of nutrients by GI bypass improves glucose tolerance only in patients with diabetes, but is detrimental for glucose homeostasis when performed in nondiabetic humans (i.e. surgical exclusion of the duodenum for the treatment of peptic ulcer or gastric cancer).[8] Therefore, T2DM might be characterized by a component of duodenal-jejunal dysfunction.

It is important to understand whether remission occurrence is an effect of changes that improve glucose homeostasis per se or as the result of reversing abnormalities of glucose metabolism. The latter implies that the GI tract itself plays a role in diabetes pathophysiology. DJB to treat diabetes in nonmorbidly obese led to insignificant weight loss, but normal glucose and A1C levels.[9] Remission of diabetes in patients who were not morbidly obese has also been reported after RYGB and BPD. A meta-analysis showed that RYGB results in an average 50–60% long-term excess weight loss; but fail to achieve complete remission of their obesity.[10] In spite of many patients remaining overweight or frankly obese more than 80 and 90% of RYGB and BPD patients, respectively have a complete sustained remission of T2DM.[10] Consider in terms of its ability to induce disease remission, RYGB (and BPD) appear more effective in treating diabetes than obesity. A recent study showed that changes in the metabolism of the Roux limb itself may play a direct role in the improvement in glucose homeostasis after RYGB by remodeling and reprogramming intestinal glucose disposal and metabolism triggered by exposure of the Roux limb to undigested nutrients.[13]

Documented studies in which long-term glycemic control had been recorded following bypass and restriction bariatric surgery in obese type 2 diabetic patients, there is evidence from both animal studies and clinical series that GI bypass procedures do not cause significant body weight loss when performed in individuals with normal body weight and body mass index (BMI). DJB can achieve adequate diabetes control in overweight patients (BMI 29–30 kg/m²) without causing significant weight loss, and BPD also has been reported to resolve T2DM in lean individuals without any weight loss.[12,13] Taking into account that mechanisms independent of weight loss contribute to diabetes control it is theoretically plausible to consider surgery as an alternative or complementary therapy to medical treatment of T2DM, even in patients with lower BMIs than conventionally accepted for bariatric surgery, up to 30 kg/m² in patients with diabetes.[14] Landmark clinical trials have consistently shown that diabetic patients have a mean BMI close to 30.[14] In recent years several groups have published encouraging results of their early experiences of metabolic surgery (novel and established techniques) in overweight or mildly obese diabetic patients with BMI < 35.[14] The authors have noted how difficult it was to treat these patients with T2DM in current clinical practice. A recent study of surgical treatment in 11 non obese (BMI < 30) diabetic patients show promising results after 1-year follow-up.[14] Using surgery explicitly to treat diabetes is a revolutionary concept and represents a major change in current therapeutic paradigms. At this time, there is no scientific evidence that any clear BMI cutoff can distinguish between patients in whom surgery can resolve diabetes and patients in whom surgery would be ineffective for this purpose. Randomized clinical studies of diabetes surgery are needed with limited BMI ranges to find better criteria for patient selection and for changing the focus from BMI to diabetes-specific parameters and the type of operation best suited to treat diabetes. Future research should focus on new surgical approaches and devices for diabetes treatment with minimal invasiveness and side effects.

In conclusion, T2DM remains a medically incurable disease and is poorly controlled in a vast majority, in spite of tremendous advancements in pharmacotherapy. A growing body of evidence, however, appears to indicate that T2DM may be an operable intestinal illness—a novel revolutionary concept about an old disease. This may facilitate research that can better clarify our understanding of the etiology of the disease and provide a new opportunity to develop
new and more effective therapies. Exploiting the changes occurring in intestinal metabolism after RYGB, future research should focus on an approach to bypass the bypass, that is, to replace the gastric bypass by equally effective, but less invasive treatments for majority of diabetics.

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