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Metabolic surgery and beta cell regeneration in type-1 diabetes: a novel hypothesis

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Abstract

Bariatric or metabolic surgery provides superior short and long-term resolution rates in subjects with Type-2 Diabetes Mellitus (T2DM) when compared to intense medical therapy. These resolution rates are more evident for so called "stapling or bypass procedures" such as the Roux-Y Gastric Bypass (RYGB) and the bilio-pancreatic diversion (BPD) with duodenal switch (DS). A recent meta-analysis demonstrated that bariatric surgery, specifically RYGB, was able to decrease insulin requirements by more than 50% in subjects with Type-1 diabetes mellitus (T1DM). These results may encourage us to rethink the patho-physiologic mechanisms of T1DM and elucidate different potential treatment options that may result in insulin independence. In contrast to the most common T2DM, where β-cell dysfunction and insulin resistance play a key role, infusion of adult stem cells with immune-modulatory properties may be of assistance to restore self-tolerance and β-cell mass in T1DM, where autoimmunity is responsible for the selective loss of β-cells. Therefore, we propose a novel hypothesis were metabolic surgery in combination with adult stem cell therapy to promote β-cell regeneration may result in insulin independence in T1DM. To our knowledge and up to date such a hypothesis has not been proposed.

Background

Bariatric surgery is a term that defines a weight loss only procedure while metabolic surgery (i.e. diabetes surgery), comprises several gastrointestinal procedures that are used with the intent to treat diabetes mellitus and other metabolic dysfunctions[1]. Metabolic surgeries have historically included procedures such as RYGB, Sleeve gastrectomy and BPD with DS. However, in the U.S. the RYGB is still considered the preferred procedure to treat obese patients with T2DM.

Metabolic surgery has shown greater short and long-term resolution rates in subjects with Type-2 Diabetes Mellitus (T2DM) when compared to intense medical therapy in several prospective randomized clinical trials[2-4]. A meta-analysis by Ashrafian et al. demonstrated that RYGB was able to reduce insulin requirements by more than 50% in Type-1 diabetes mellitus (T1DM)[5].

Up to date, very few of the proposed mechanisms of resolution of T2DM after metabolic surgery in obese subjects have been elucidated. Therefore, it is intuitive to generalize some of these mechanistic pathways to other types of diabetes with a very different underlying patho-physiology such as T1DM. The significant metabolic results obtained with metabolic surgery should not be ignored as well as the benefits of intestinal bypass reconstructions on insulin sensitivity and pancreatic β-cell function that leads to insulin independence and the long-term remission of T2DM.

Hypothesis

Metabolic surgery (Roux-Y gastric bypass) in conjunction with intraperitoneal implantation of **A**dult **Stem** Cells to promote β-cell regeneration may provide insulin independence in T1DM (METASTEM study).

Basis of the Hypothesis

Type-2 diabetes is commonly associated with severe obesity. The main patho-physiologic characteristics of T2DM are peripheral insulin-resistance with

progressive pancreatic β-cell loss, which may result in insulin dependence. A lipocentric theory has described this insulin resistance and β-cell loss, as being secondary to the metabolic trauma caused by ectopic multi-organ lipid deposition or lipotoxicity that results during severe obesity states[6].

In recent years, metabolic surgery has shown to effectively provide short and long-term remission of T2DM in obese individuals and has proven superior to intense medical therapy[2-4]. However, the results of metabolic surgery on T1DM are still scarce. Several hypotheses have supported the use of the RYGB procedure, in which a complete duodenal-jejunal exclusion is performed[7]. In T2DM patients, the exclusion of the duodenum and proximal jejunum has been shown to provide enhanced incretin and anti-incretin effects with improvements in both insulin sensitivity and pancreatic β-cell function[8].

Various types of intestinal reconstructions in metabolic surgery have proven effective in the treatment of non-obese and mildly obese patients with T2DM. The duodeno-jejunal exclusion that explains in part the T2DM remission after RYGB Metabolic Surgery could be extrapolated to T1DM. An elongated bilio-pancreatic limb reconstruction may be able to further augment this incretin activity and β-cell trophic factors (mainly by GLP-1, GIP and PYY effects).

We have previously proposed that the key component of this RYGB metabolic surgery is the lengthening of the bilio-pancreatic limb and not the alimentary limb (a 150-150 cm reconstruction respectively)[9] (Figure 1). The incretin effects of this elongated bilio-pancreatic limb RYGB may explain in part the existence of a entero-pancreatic axis as described by Kamvissi et al[8]. There may be other various hormonal or paracrine pathways involved that still need to be elucidated. We have also previously demonstrated that this type of anatomic reconstruction RYGB is capable of providing remission and insulin independence in pancreatogenic diabetes after subtotal pancreatectomy[10].

On the other hand, T1DM is a disease characterized by the autoimmune destruction of insulin producing β-cells. The disease spectrum encompasses a series of autoantibodies directed toward the islet cells, followed by T cell mediated β-cell destruction and insulin dependence. T1DM is more frequent in childhood and adolescents but

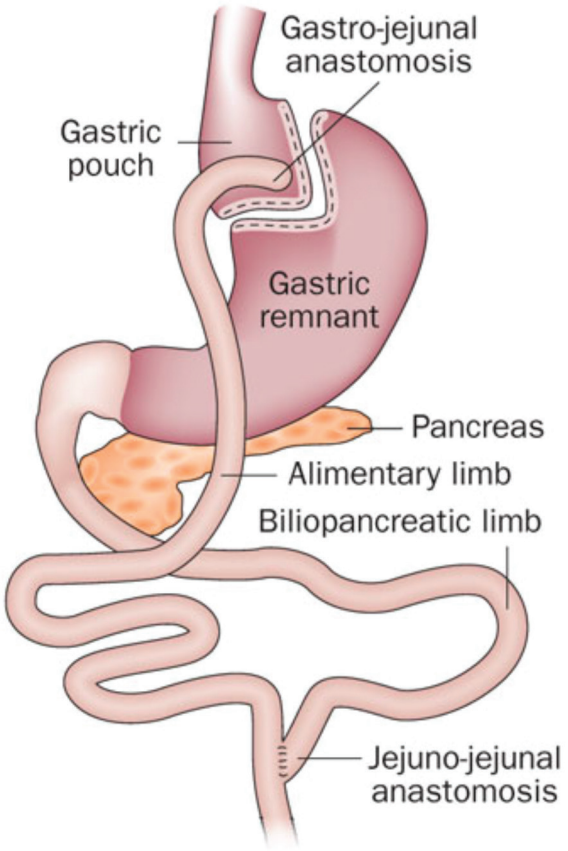

Figure 1. Roux-Y gastric bypass reconstruction.

can occur at any age throughout adulthood. It is also possible that a small percentage of obese patients are mislabeled as T2DM when in reality they belong to the T1DM spectrum, with associated severe obesity and may present with clinical manifestations of both diabetes types (i.e. auto-antibodies, insulin resistance and insulin dependence).

The evidence regarding the effects of Metabolic Surgery on T1DM is not well documented and it is limited to few case reports and small case series[11,12]. Nevertheless, in a recent meta-analysis involving 27 studies and 142 T1DM patients undergoing mainly RYGB, metabolic surgery provided significant reductions in insulin requirements by 50% or more, as well as significant decreases in HgA1c and body mass index[5]. In addition, metabolic surgery also provided significant improvements in blood pressure and lipid profile in patients with T1DM.

These improvements in insulin requirements cannot be explained if the pathophysiology of T1DM is exclusively autoimmune in nature, with complete β-cell destruction, as Metabolic Surgery

has been linked not only with improvements in insulin sensitivity and β-cell function but with β-cell regeneration, hyperplasia, anti-inflammatory and immunomodulatory mechanisms that could improve autoimmune conditions. Furthermore, there is evidence that a number of T1DM patients are in reality insulin micro-secretors and still have functional β-cells that may be amenable to stimulation and regeneration. It is possible that all these variables may play a role in T1DM following metabolic surgery, and could be of assistance to explain the significant decrease in insulin requirements observed following surgery.

The beneficial effects of metabolic surgery on T1DM should encourage the rethinking of a new paradigm regarding the patho-physiology and treatments for T1DM. Hence, metabolic surgery may become in the future part of the armamentarium as a multi-modal strategy for treatment of T1DM. This multi-modal approach should address issues inherent to T1DM such as immunomodulation and the scarcity and functional integrity of β-cell mass.

Great strides have been made in the area of islet cell transplantation however the long-term survival of these allografts has been discouraging not to mention high related costs, long term immunosuppression and shortages in donor pancreas[13]. Most recently, Ricordi and collaborators reported a successful extrahepatic allogeneic islet cell implantation with a biologic 3D scaffold in the omentum, which could result in improved islet transplant outcomes[14].

The area of stem cell regeneration therapy with autologous adult mesenchymal stem cells (MSCs) opens a new horizon for immunomodulation and pancreatic cell regeneration, which may address the much-needed pieces in the puzzle of T1DM treatment.

Several advances in stem cell therapy have been attained with autologous adult stem cell types. Stem cells are pluripotent cells of mesenchymal origin that have the potential to differentiate, when properly stimulated, into different cell lines including endodermic pancreatic β-cells lines and clusters. Autologous adult stem cells offer several advantages over embryonic ones including lack of immunohistocompatibility issues or graft rejection, no need for systemic immunosuppression therapy, easier procurement, plenty of availability in adult donor sites, lower costs and less ethical, religious and regulatory approval concerns. Furthermore, the FDA has approved many autologous adult MSCs for other clinical indications. The most commonly MSCs procured are those from bone marrow, adipocyte tissues, umbilical cord, and placenta, among others.

Adult MSCs have immune-modulatory properties that are capable of impairing the immune dysregulation that leads to insulin producing cells destruction in T1DM. Mesenchymal stem cells have also been found to secrete anti-inflammatory cytokines in diabetic conditions and have other immune-modulatory therapeutic applications. They also have regenerative and reparative properties that make them potential candidates to regenerate insulin-producing cells. Furthermore, transplanted MSCs in T1DM patients without immunotherapy have been shown to improve metabolic function[15]. Cotransplanted MSCs have also been shown to contribute to the regeneration of insulin-producing pancreatic cells. Most of the recent approaches successfully differentiated MSCs along the insulin-producing cells lineage and have reversed hyperglycemia in vivo. The ideal MSCs donor and implantations sites that will be able to yield and sustain insulin-producing cells have yet to be determined.

Evaluation of Hypothesis

It is now known that metabolic surgery has the potential to significantly decrease insulin requirements in T1DM. Hence, metabolic surgery and stem cells should be considered as part of a multi-modal treatment algorithm for T1DM treatments. This protocol requires a multidisciplinary team approach and infrastructure including metabolic surgeons, endocrinologists, immunologists, and regenerative medicine specialists.

In the METASTEM protocol, adult and non-obese patients with a diagnosis of T1DM will undergo RYGB as Metabolic Surgery with 150 cm alimentary and bilio-pancreatic limbs respectively. Approximately 6 months after metabolic surgery when insulin requirements have decreased significantly, patients will undergo bone marrow harvesting for stem cell procurement and processing through a U.S. Patent Pending process. This time interval will allow optimization of the patient's metabolic profile (i.e. insulin and glucose toxicity), which may improve the MSCs chances of survival. Stem cells will then be implanted intraperitoneal within the liver and pancreatic beds, root of mesentery and omentum with a biodegradable scaffold and under

direct vision via laparoscopic techniques. Primary endpoints will include pre and post-prandial glucose, insulin and C-peptide levels. Clinical trials evaluating metabolic surgery in combination with MSCs for the treatment of T1DM are currently undergoing at our Institute.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

References

1. Rubino F, Shukla A, Pomp A, Moreira M, Ahn SM, Dakin G. Bariatric, metabolic, and diabetes surgery: what's in a name? Ann Surg 2014; 259: 117-122.
2. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Nanni G, Castagneto M, Bornstein S, Rubino F. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2015; 386: 964-973.
3. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012; 366: 1577-1585.
4. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B, Nissen SE, Bhatt DL. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012; 366: 1567-1576.
5. Ashrafian H, Harling L, Toma T, Athanasiou C, Nikiteas N, Efthimiou E, Darzi A, Athanasiou T. Type 1 diabetes mellitus and bariatric surgery: a systematic review and meta-analysis. Obes Surg 2015 Dec 22. [Epub ahead of print].
6. Unger RH. Reinventing type 2 diabetes: pathogenesis, treatment, and prevention. JAMA 2008; 299: 1185-1187.
7. Rubino F, Forgione A, Cummings DE, Vix M, Gnuli D, Mingrone G, Castagneto M, Marescaux J. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg 2006; 244: 741-749.
8. Kamvissi V, Salerno A, Bornstein SR, Mingrone G, Rubino F. Incretins or anti-incretins? A new model for the "entero-pancreatic axis". Horm Metab Res 2015; 47: 84-87.
9. Chaux F, Bolanos E, Varela JE. Lengthening of the bilio-pancreatic limb is a key step during revisional Roux-Y gastric bypass for weight regain and diabetes recurrence. SOARD 2015.
10. Chaux F, Franco M, Varela JE. Metabolic surgery provides remission of pancreatogenic diabetes in a non-obese patient. SOARD 2015.
11. Brethauer SA, Aminian A, Rosenthal RJ, Kirwan JP, Kashyap SR, Schauer PR. Bariatric surgery improves the metabolic profile of morbidly obese patients with type 1 diabetes. Diabetes Care 2014; 37: e51-2.
12. Lannoo M, Dillemans B, Van Nieuwenhove Y, Fieuws S, Mathieu C, Gillard P, D'Hoore A, Van Der Schueren B. Bariatric surgery induces weight loss but does not improve glycemic control in patients with type 1 diabetes. Diabetes Care 2014; 37: e173-4.
13. Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, Alejandro R, Ryan EA, DiMercurio B, Morel P, Polonsky KS, Reems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DE, Eisenbarth G, Segal M, Preiksaitis J, Korbutt GS, Barton FB, Viviano L, Seyfert-Margolis V, Bluestone J, Lakey JR. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006; 355: 1318-1330.
14. Pedraza E, Brady AC, Fraker CA, Molano RD, Sukert S, Berman DM, Kenyon NS, Pileggi A, Ricordi C, Stabler CL. Macroporous three-dimensional PDMS scaffolds for extrahepatic islet transplantation. Cell Transplant 2013; 22: 1123-1135.
15. Cai J, Wu Z, Xu X, Liao L, Chen J, Huang L, Wu W, Luo F, Wu C, Pugliese A, Pileggi A, Ricordi C, Tan J. Umbilical cord mesenchymal stromal cell with autologous bone marrow cell transplantation in established type 1 diabetes: a pilot randomized controlled open-label clinical study to assess safety and impact on insulin secretion. Diabetes Care 2016; 39: 149-157.