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Influences of the diabetes surgery on pancreatic β-cells mass

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Abstract

In diabetes mellitus type 2 (DMT2), malfunction and apoptosis of β-cell provoke a deficient insulin secretion. Generally, has been sustained that β-cell function is severely compromised in type 2 diabetes before the disease appears and then continues to decrease linearly with time. Diversionary bariatric procedures such as gastric bypass, biliopancreatic diversion, one anastomosis gastric by-pass (BAGUA) and others that bypasses the foregut, induce a rapid non-weight-loss-associated improvement in glycemic control, especially if treated early before irreparable β-cell damage has occurred. The antidiabetic effect of bariatric operations is likely due to the improvement in the hormonal dysregulation associated with the development of diabetes. Now we know that the bariatric surgery through the reorganization of the gastrointestinal tract can affect to β-cells mass homeostasis, stopped apoptosis and stimulate the replication and neogenesis. These effects are caused mainly by three stimuli: caloric restriction, rapid transit of food to the ileum and the exclusion of an intestinal portion including the stomach, duodenum and part of the jejunum. Several mechanisms have been proposed for this exciting effect that may provide key insights into the pathogenesis of type-2 diabetes. All of these mechanisms include from gut hormones such as ghrelin to second messengers such as AKT system or protein kinase B. Although not all the processes involved in the homeostasis of β-cells are clear, we can explain some of the effects of bariatric surgery exerted on this important set of endocrine cells, which are essential in diabetes control.

(Key words: Bariatric surgery. Pancreas β-cells. Diabetes mellitus.)
Introduction

β-cell mass regulation represents a critical issue for understanding diabetes, a disease characterized by a deficiency in the number of pancreatic β cells. The number of islet β cells present at birth is mainly generated by the proliferation and differentiation of pancreatic progenitor cells, a process called neogenesis. Shortly after birth, β-cell neogenesis stops and a small proportion of cycling β cells can still expand the cell number to compensate for increased insulin demands, but at a slower rate. The low capacity for self-replication in the adult is too limited to result in a significant regeneration following extensive tissue injury. In addition, chronically increased metabolic demands can lead to β-cell failure to compensate. Neogenesis from progenitor cells inside or outside islets represents a more potent mechanism leading to robust expansion of the β cell mass, but it may require external stimuli. Recent studies have demonstrated that it is possible to regenerate and expand the β-cell mass using hormones and growth factors like glucagon-like peptide-1, gastrin, epidermal growth factor, and others. Treatment with these external stimuli can restore a functional β-cell mass in diabetic animals.

Malfunction and β-cell apoptosis

The triggering factor in DMT2 is β-cell failure, which involves a decrease in β cell mass and deterioration of key β cell functions such as glucose-stimulated insulin secretion (GSIS). We know that obesity often leads to insulin resistance, but not all obese people develop DMT2. Likewise, we can also see how normal weight people develop insulin resistance just as obese. A study comparing the β cell mass in obese diabetic/obese nondiabetic note that β cells was decrease in individuals with T2DM. Similarly, β cell apoptosis is increased in obese humans with glucose intolerance or diabetes. Genetic background has an important role in determining the susceptibility of β cells to decompensation and progression to DMT2. This is demonstrated using rodent models. Genes responsible for obesity and insulin resistance interact with environmental factors (increased fat/caloric intake and decreased physical activity), resulting in the development of obesity and insulin resistance. These increase secretory demand on β-cells. If the β-cells are normal, their function and mass increase in response to this increased secretory demand, leading to compensatory hyperinsulinaemia and the maintenance of normal glucose tolerance. By contrast, susceptible β-cells have a genetically determined risk, and the combination of increased secretory demand and detrimental environment result in β-cell dysfunction and decreased β-cell mass, resulting in progression to impaired glucose tolerance, followed, ultimately, by the development of DMT2.

The mechanisms through death in the β cell occurs are related to work overload in the endoplasmic reticulum (ER) and constitutive upregulation of pyruvate cycling that affects the performance of the mitochondria and glucose sensitivity. Overnutrition and increased lipid supply induce enzymes of beta-oxidation, such as carnitine palmitoyltransferase-1 (CPT1), resulting in increased acetyl CoA levels, allosteric activation of pyruvate carboxylase (PC) and deregulation of pyruvate cycling. This leads to basal insulin hypersecretion and loss of the glucose-stimulated increment in pyruvate cycling flux, thereby blunting glucose stimulated insulin secretion. Finally, insulin hypersecretion is accompanied by amylin secretion, which in humans can form amyloid fibrils that accumulate at the surface of β-cells to induce dysfunction and apoptotic death.

The increased demand for insulin biosynthesis increases demand (workload) in the ER, gradually leading to ER stress and increased protein misfolding. ER stress is initially relieved by the unfolded protein response (UPR), mediated by the transcription factor XBP1, but over time, the UPR becomes less effective and the deleterious effects of ER stress lead to cell death, mediated by IRE1.

AKT cell signaling system is involved in the apoptosis process, in a crucial way. This signaling system is activated through receptors on the cell surface. When
activated induces the production of second messengers as PIP3, phosphatidylinositol 3,4,5-triphosphate, which carries the signal from the cell surface to the cytoplasm. PIP3 activates the serine/threonine kinase PDK1 (3-phosphoinositide-dependent protein kinase-1) enzyme, which is able to return activated protein kinase B or AKT. The proteins phosphorylated by protein kinase B promote cell survival and its unphosphorylated form promotes apoptosis.

Regeneration of β-cells

In the remission of T2DM is obvious to think that the recovery of β-cell mass is an important factor. But seems clear that pancreas has a slow rate of β-cell turnover. Whereby β-cells replicate and new islets are formed, probably from exocrine duct cells through the process of neogenesis.11,14 The rate of β-cell replication seems to slow with age and neogenesis can be stimulated by injury. We can cause a chemical damage by administration of streptozotocin or alloxan, two drugs that destroy the β-cell selectively. Another way to study pancreas regeneration is causing tissue damage by surgery, in this case a partial pancreatectomy (70%) or subtotal (90-95%) can be performer. Otherwise, we can use duct ligation like model of tissue injury. In all experiments, an increase in the mitotic ability of the pancreas occurs after tissue damage, producing a partial regeneration of the endocrine and exocrine pancreas.11 Depending experimental model used, it is observed a higher or lower increase in β-cell replication rate, indicating that endocrine regeneration is caused by a replication increased, similar to observed in the physiological increase which occurs during adult growth. However, in other cases is observed an increase in replication rate of pancreatic ducts and it is possible to measure Pdx-1 expression and insulin in ductal cells.11 This suggests that in these cases regeneration is produced by a neogenesis activation, through the stem cells or precursor cells activation. The results indicate that these cells will differentiate to β-cell using the same molecular mechanisms that occur during embryogenesis. Moreover it has been demonstrated that exist several substances able to stimulate regenerative processes when administered to animal models. GLP1 promotes the proliferation and neogenesis of β-cells, reduces β-cell apoptosis, and increases differentiation of exocrine-like cells toward a more differentiated β-cell phenotype.12 The betacellulin, EFGs (epidermal growth factor) growth factor family promotes the regeneration of β-cells in both rats and mice pancreatectomized perfused with alloxan.13 Also the combination of different factors such as gastrin and EGF, induce β-cell growth in mice treated with alloxan or in mice with a duct ligation.14 Therefore, we could think that if bariatric surgery is able to stimulate some of these hormones secretion will be able to activate cells replication and neogenesis (small scale).

Bariatric surgery types

Not all bariatric procedures have the same effect on weight loss and diabetes remission, certain procedures are more effective than others and its effect occurs a few days after the intervention. The two major types are classified as purely restrictive procedures and a mix of restrictive and malabsorptive procedures; last one technique includes an intestinal bypass. Purely restrictive procedures (laparoscopic adjustable gastric banding, sleeve gastrectomy, vertical gastroplasty) limit gastric volume and, therefore, restrict the intake of calories by inducing satiety. Afterward, patients lose approximately 10% to 20% of their total body weight. Furthermore, multiple studies, including a randomized controlled trial,15 have shown remission of type 2 diabetes with these techniques but not with conventional medical therapy. The effect is primarily mediated by weight loss and improved insulin sensitivity, both of which occur several months following surgery. On the other hand, a second category described as intestinal bypass procedures, that include one anastomosis gastric bypass (BAGUA), gastric bypass Y-Roux, biliopancreatic diversion, and other techniques derived from these, have a different mechanism of action. The stomach is partitioned, with the proximal portion then connected to the jejunum. The distal portion of the stomach, duodenum and early jejunum is then connected downstream from the gastrojejunal anastomosis to the mid to distal jejunum. In this type of intervention, type 2 diabetes often resolves within days or weeks after surgery, long before that a significant weight loss has occurred.16,17

Bariatric surgery effects

Intestinal reconfiguration provokes by BAGUA, BPD and RYGB procedures causes different stimuli on the gastrointestinal tract. These stimuli are due to the effect of caloric restriction, exclusion of a great part of the stomach and duodenal bypass. Causing, in the case of by-pass, a rapid transit of food through the gut and avoiding contact with that intestinal portion. These effects are related to the rapid remission of T2DM.18

Caloric restriction

This effect is produced by the resection of a large part of the stomach, limiting food intake. Caloric restriction lowers blood sugar, resulting in a decrease in insulin secretion. This reduces lipogenesis in white adipose tissue (WAT), thereby decreasing the production of TNFα and increases adiponectin, enhancing
insulin sensitivity in metabolically active tissues such as muscle and liver, again decreasing blood glucose levels.\(^\text{36}\) Some studies relate caloric restriction with expression of SIRT-1.\(^\text{1,3}\) This protein, a homolog of the yeast protein silent information regulator 2 (Sir2), which encodes an NAD\(^+\) (nicotinamide adenine dinucleotide) dependent histone deacetylase may play a key role in the regulation of β-cell apoptosis. SIRT1 is only expressed in islets, but not in the exocrine function of islets. The SIRT1 binding promoter region of uncoupling protein 2 (UCP2) directly represses the expression of the UCP2 gene and regulates glucose-stimulated insulin secretion (GSIS). Increased SIRT1 expression significantly promotes GSIS. According to the physiological functions of SIRT1 substrates and the special effects of SIRT1 in islet β-cells, it is reasonable to believe that SIRT1 expression is not only involved in regulating β-cell function to secrete insulin, but also is associated with the apoptosis of β-cells. SIRT1 inhibits β-cells apoptosis by repressing the UCP2 gene transcription (mitochondrial uncoupling protein), increasing mitochondria energy efficiency and release of the endoplasmic reticulum stress. However, transcription repression of UCP2 by SIRT1 appears to be counteracted during the fast, slowing the synthesis of ATP and insulin response, possibly by a ratio NAD/NADH decrease in the pancreas. SIRT1 also could promote beta-cells survival during oxidative stress by FOXO1 and subsequent activation of transcription factors NeuroD and Mafa, increasing resistance to stress.\(^\text{24}\) FOXO1 activates by SIRT1 also involved in the regulation of glucose, promoting gluconeogenic gene transcription during stress.

*Ghrelin levels decreased?*

Ghrelin is a 28-amino acid orexigenic hormone secreted from the duodenum and stomach. In addition to contribute to marked decrease in appetite and food intake observed after bariatric surgery, ghrelin may also improve glucose tolerance. Ghrelin may stimulate insulin-regulating hormones, suppress adiponectin (a hormone insulin sensitizer), decreased hepatic insulin sensitivity at the level of phosphatidyl inositol-3-kinase and inhibit the secretion of insulin by β-cells.\(^\text{13}\) The physiological significance of ghrelin as inhibitor of insulin secretion was demonstrated in a study of ghrelin-deficient mice\(^\text{10}\) which showed low levels of uncoupling protein 2 (UCP2) in pancreatic islets. As seen above, the decrease in the levels of this protein leads to increased insulin secretion and inhibition of β-cell stress, thus improving their survival and function. These mice showed greater sensitivity to insulin and improved glucose tolerance that the mice able to synthesize ghrelin.\(^\text{10}\) Because 90% of ghrelin synthesis is performed on that portion of the intestinal tract, which has been excluded from the stimulus of food, is feasible to believe that compromise secretion of ghrelin may contribute to antidiabetes effects of bariatric surgery.\(^\text{5}\) Ghrelin levels after these procedures were extremely low throughout the 24-h period, a paradoxical response in the face of profound weight loss. Since then, eight other groups have shown in prospective studies that ghrelin levels fall after bariatric surgery (or at least are more suppressed by food intake), and four cross-sectional studies have confirmed abnormally low levels in operated patients compared with controls.\(^\text{28}\) Three other groups found no significant change in human ghrelin levels after bariatric surgery but interpreted this as impairment in the expected increase of ghrelin with weight loss. In contrast, four groups have reported normal increases in ghrelin with surgery induced weight loss. These heterogeneous findings suggest that differences in surgical techniques, possibly involving treatment of the vagus nerve,\(^\text{5}\) might account for the disruption of ghrelin secretion in most but not all cases.

*Rapid transit of food*

The result of this effect is an unabsorbed nutrients increase in the distal intestine, enhancing the release of GLP-1 by L cells, thus improving glucose homeostasis. The original physiological role described for GLP1 was like an incretin hormone that stimulates insulin secretion in a glucose-dependent manner.\(^\text{33}\) GLP1 also increases transcription of the gene encoding insulin and enhances both the stability of the mRNA encoding insulin and biosynthesis of insulin by mechanisms that involve pathways that are both dependent on and independent of cAMP and protein kinase A, as well as pathways that increase the intracellular concentration of Ca\(^{2+}\). In addition, GLP1 improves β-cell function by inducing the expression of sulfonlurea receptor and inwardly rectifying K+ canal (KIR6.2) in β-cells. It also prevents the downregulation of ATP-sensitive K+ channel activity induced by high levels of glucose. GLP-1, with PYY and oxyntomodulin are synthesized in the ileum and colon through stimulation of L cells by nutrients. After BPD, the food goes directly from the stomach to the ileum and GLP-1 levels appear unquestionably high. This effect may be less obvious in the case of RYGB because the intestinal bypass is lower. However, have been measured elevated levels of GLP-1, PYY and oxyntomodulin in both types of bariatric surgery.\(^\text{35}\) Further support for the effect of rapid transit, comes from ileal interposition procedure. In this type of surgery, a segment of the L-cell-rich ileum is transplanted into the upper interposition near the duodenum-jejunum boundary, thereby increasing its exposure to ingested nutrients. This reconfiguration of the digestive tract provoke a greatly enhances postprandial GLP-1 and PYY levels. Ileal
interposition with no gastric restriction or malabsorption, results in improved glycemic control, with or without weight loss depending on the rodent model or humans studied. It is unclear the main process through which it enhances the insulin secretion, as predicted from increases in the incretin GLP-1, or improves insulin sensitivity, and the results of different experiments support both possibilities.

The exclusion of the intestinal segment

Several studies in rats have demonstrated that exclusion of the proximal small intestine from contact with ingested nutrients is a critical component in the mechanism improving glucose tolerance after bariatric operations that bypass the proximal small intestine. Dr. Francesco Rubino, with his model of duodenal-jejunal bypass (DJB), was the first to provide strong evidence supporting this model. In this variant of RYGB, the stomach remains intact but excludes the proximal intestine of food contact. In Goto-Kakizaki rats (GK), used as an experimental animal model of T2DM without obesity, this operation improves diabetes quickly and permanently, even without reduction in food intake or weight loss. GK rats subjected to DJB with duodenal exclusion followed by DJB without duodenal exclusion, or vice versa, experienced reversible remission and reconstitution of T2DM. Diabetes was eliminated or restored based on the absence or presence, respectively, of nutrient passage through the duodenum. To try to explain these results we must return to the increase in GLP-1 synthesis measured after bariatric surgery with duodenal bypass, which seems to have, as we explained before, an important role in maintaining β-cell mass. The initial rapid rise in GLP-1 secretion must be mediated indirectly, through a neuro/endocrine pathway, rather than through direct interactions of the luminal contents with L-cells. Figure 2 shows GLP-1 secretion regulation by neuro/endocrine pathway. After a meal, nutrients in the duodenum activate a proximal-distal neuroendocrine loop, which stimulates GLP-1 secretion from L-cells in the ileum and colon. In rodents, GIP, released from K-cells, activates vagal afferents, which subsequently causes GLP-1 secretion through vagal afferents and enteric neurons that release acetylcholine (Ach) and peptide release gastrin (GRP). Movement of nutrients toward more distal sections of the intestine leads to the direct interaction of nutrients with L-cells, which also stimulates GLP-1 secretion. Placement glucose or fat into the duodenum of rodents, which were prevented nutrients contact to the ileum, which excluded the possibility of direct interaction between luminal nutrients and L-cells, induced an immediate and prolonged stimulation of the L-cell that was comparable in magnitude to increments in GLP-1 observed when nutrients were placed directly into the ileum. Furthermore, when nutrients were placed in the duodenum of the rat, a prompt rise in glucose-dependent insulinotropic peptide (GIP) levels was also observed, and infusion of GIP or treatment of primary rat L-cells in culture with GIP also stimulated GLP-1 secretion, thus implicating GIP in the proximal regulation of GLP-1 secretion. The more important role of the vagus nerve in mediating the proximal-distal

Fig. 2.—GLP-1 secretion regulation by neuroendocrine pathway.
loop was elucidated when L-cell stimulation by placement of fat into the duodenum or by infusion of physiological concentrations of GIP was completely abrogated by sub-diaphragmatic vagotomy. 46

Summary

The studies summarized in this article have greatly advanced our understanding of the molecular and biochemical mechanisms that are involved in the development of type 2 diabetes. In morbid obesity, bariatric surgery with duodenal and proximal jejunal bypass causes rapid and profound metabolic adaptations; insulin sensitivity improves in proportion to the weight loss, and β-cell glucose sensitivity increases independently of weight loss. Furthermore the improvement of glucose homeostasis is greater after this surgery than after other weight loss methods. The mechanisms involved in the remission of T2DM include: 1) caloric restriction, which through the SIRT1 protein, inhibits β-cell apoptosis by repressing UCP2 gene transcription (mitochondrial uncoupling protein), increased mitochondrial energy efficiency and the release of endoplasmic reticulum stress. 2) Possible compromised ghrelin secretion in some cases, with decrease in the levels of UCP 2, which leads to increased insulin secretion and inhibition of β-cell stress, thus improving their survival and function. 3) Enhanced nutrient stimulation of L-cell peptides from the lower intestine provokes a GLP-1 levels increase. This protein, increases transcription of the gene encoding insulin and enhances both the stability of the mRNA encoding insulin and biosynthesis of insulin, improve the beta-cells survival. 4) Exclusion of the upper intestine from contact with ingested nutrients that provoke again GLP-1 increased levels, this time by neuro/endocrine pathway. Moreover, these mechanisms cause deregulations in many hormones and second messengers levels, all related to glucose homeostasis, survival and regeneration of beta cells, and probably additional unknown effects. Characterization and identification of other contributing factors are compelling research objectives that promise not only to guide surgical design but also to reveal novel targets for pharmacological therapy of diabetes. Molecular biology tools including global gene expression analysis and proteomics should be applied on tissue biopsies and isolated cell fractions collected before and shortly after bariatric surgery. Since certain biopsies are difficult to obtain from humans, the rat may be a useful model for studying the acutest well as long-term metabolic effects of bariatric surgery in all tissues.44, 45

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