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Role of the bypassed proximal intestine in the anti-diabetic effects of bariatric surgery

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Among the panoply of obesity-related co-morbidities that are ameliorated by bariatric surgery, perhaps the most impressive and scientifically interesting is the rapid, dependable resolution of type 2 diabetes. Numerous studies, including a meta-analysis of 22,094 patients, confirm that 83% to 86% of patients with diabetes experience complete remission of their disease after Roux-en-Y gastric bypass (RYGB), subsequently manifesting normal blood glucose and hemoglobin A1c levels after discontinuation of all diabetes medications [1–5]. After biliopancreatic diversion (BPD), the remission rate is greater than 95% [1]. The relatively few patients whose diabetes does not completely resolve after these procedures have typically had their disease for many years [3], and the progressive β -cell failure characteristic of longstanding type 2 diabetes has presumably rendered these individuals' pathology irreversible.

What mechanisms could mediate such a profound improvement in diabetes, which is traditionally considered a relentless, progressive disease? The answers to this question could yield insights leading to the discovery of novel diabetes medications. Undoubtedly, massive weight loss plays an important role, especially in consolidating the long-term antidiabetic effects. After bariatric surgery, many physiologic changes have been documented that should improve glucose homeostasis. These include increases in muscle insulin receptor density and adiponectin levels, as well as decreases in the intramuscular and intrahepatic content of total lipids and long-chain fatty acyl-CoA molecules (moieties that cause insulin resistance) [6–8]. As predicted from these changes, glucose transport in incubated muscle fibers, whole-body glucose disposal during euglycemic clamps, and insulin sensitivity as measured by minimal modeling all increase dramatically after RYGB-induced weight loss [6,8,9]. BPD improves insulin sensitivity even more than does RYGB [10]. These adaptations, however, have been recorded many months to years after surgery. Because they would be predicted to occur as a consequence of substantial weight loss achieved by any means, such changes do not distinguish the impact on diabetic parameters of bariatric surgery per se from secondary results of weight loss.

The most dramatic observation in this arena is that certain bariatric operations cause complete remission of diabetes within days to weeks after surgery—long before substantial weight loss

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has occurred [3,11]. This remarkable phenomenon suggests that mechanisms beyond just weight loss contribute to the antidiabetic effects of some procedures; acquiring a thorough understanding of this physiology is an important research priority. Among the several hypotheses that have been invoked to explain this rapid postoperative resolution of diabetes, a key role for the nutrient-excluded proximal small intestine has recently come into focus, largely due to rodent experiments pioneered by Dr. Francesco Rubino. A report by Cohen et al. [12] in this issue of *SOARD* takes the first step toward extending these scientific findings into the clinical realm. The authors describe resolution of diabetes, without any weight loss, in 2 patients who underwent a stomach-sparing bypass of a short segment of proximal small intestine, equivalent to the amount bypassed with a typical, conservative RYGB.

Before discussing the effects of proximal intestinal exclusion on glucose homeostasis, however, let us consider some other potential antidiabetic mechanisms of bariatric surgery. A rather pedestrian, though not unreasonable hypothesis is that diabetes resolves because of immediate postoperative starvation, followed by rapid weight loss. According to this model, diabetes might initially remit after surgery because β cells are challenged with little or no ingested nutrients during that period. Thereafter, by the time patients' early postoperative dietary restrictions have been lifted, they begin to experience the insulin-sensitizing effects of active weight loss resulting from the bariatric operation. Given the known effects of acute starvation and active weight loss to improve diabetes, this hypothesis does have merit. If it were the only mechanism at work, however, one would predict that adjustable gastric banding (AGB) would yield similar antidiabetic effects as do RYGB and BPD. All 3 procedures involve immediate postoperative food deprivation followed by a slow advancing of the diet, and thereafter a period of steady weight loss. Yet diabetes resolves in only 48% of cases after AGB, compared with 84% and >95% after RYGB and BPD, respectively [1]. More importantly, resolution of diabetes after AGB occurs over many weeks to months, consistent with the consequences of weight loss, whereas the effect is nearly immediate after the other 2 procedures—considerably before substantial weight loss has occurred [3]. These observations suggest that something special, beyond just short-term starvation followed by steady weight loss, occurs with regard to glucose homeostasis after RYGB and BPD.

Consistent with this notion are increasing reports of rare cases of extremely overactive pancreatic β cells after RYGB, causing life-threatening hyperinsulinemic hypoglycemia [13–16]. An illuminating feature of this phenomenon is that it typically develops several years after the operation, well after people have attained their nadir body weight and begun to regain some weight, presumably with an attendant recrudescence of insulin resistance. The implication of such late-onset hypoglycemia is that something about the post-RYGB milieu continues to stimulate β -cell function and possibly cell growth for many years—a phenomenon that is, in all likelihood, highly beneficial for the vast majority of patients with diabetes but, in rare instances, goes too far.

One possible explanation for the effects of bariatric surgery on glucose homeostasis is that the operations that create physical shortcuts for ingested nutrients to reach the distal intestine improve glucose homeostasis by augmenting secretion of glucagon-like peptide-1 (GLP-1), a nutrient-stimulated, glucose-lowering incretin hormone that is secreted from L cells primarily in the ileum and colon [17]. These same L cells also secrete peptide YY and oxyntomodulin in response to ingested nutrients. All 3 peptides are implicated in the reduction of food intake and upper gastrointestinal motility caused by the “ileal brake,” and exogenous administration of each of them promotes weight loss. Thus, expedited delivery of nutrients to the distal intestine after selected bariatric operations could contribute to weight loss in addition to diabetes resolution by hyperstimulating secretion of L-cell hormones.

The term “hindgut hypothesis” has been used to describe this notion that the effects of some bariatric operations result, in part, from enhanced nutrient delivery to the distal intestine, accentuating L-cell secretion of anorexigenic and antidiabetic peptides. The counterpart “foregut hypothesis” (discussed below) proposes that surgical exclusion of ingested nutrients from the proximal small intestine exerts antidiabetic and possibly weight-reducing effects. Although we have promulgated these terms ourselves in previous writings [18–21], we have come to understand that both expressions are misleading. The ileum is a key participant in the former model, yet it is part of the midgut, not the hindgut. The latter model focuses primarily on the duodenum, with no role for the several other foregut structures. Moreover, all published experiments supporting this foregut hypothesis have involved surgical exclusion of not only the duodenum but also part of the proximal jejunum, which is a midgut structure. Accordingly, we propose that the terms “foregut hypothesis” and “hindgut hypothesis” be replaced with “upper intestinal hypothesis” and “lower intestinal hypothesis”. Although these labels are less snappy than their predecessors, they are more accurate.

As for the lower intestinal hypothesis, because only a relatively short segment of upper intestine is bypassed in a typical proximal RYGB, it is not obvious that circumventing this minor length of intestine is sufficient to accentuate GLP-1 secretion. Moreover, GLP-1 is released not only in response to direct L-cell exposure to luminal nutrients but, perhaps more importantly, under normal circumstances it also responds to nutrients in the duodenum that activate neural and hormonal signals relayed from the proximal to the distal intestine [22]. The latter mechanism is eliminated after bariatric procedures that remove the duodenum from digestive continuity, such as RYGB. Thus, theoretically, this operation might decrease GLP-1 secretion. A recent set of publications, however, has clarified that proximal RYGB does indeed markedly accentuate postprandial responses of GLP-1 and other L-cell hormones, such as PYY [23–28]. The post-RYGB increase in GLP-1 release would be predicted to improve glucose homeostasis by accentuating glucose-dependent insulin secretion, increasing β -cell mass (at least in animals), and possibly heightening insulin sensitivity [29–31]. Many if not all of the beneficial effects of GLP-1 on glucose homeostasis and body weight involve critical vagus-nerve pathways [32]. The GLP-1 that is released in excess after RYGB and certain other bariatric operations emanates from its normal sites of synthesis. Hence, it should fully engage these neural circuits and thereby exert a greater impact on diabetes and body weight than do medicinal GLP-1 agonists such as exenatide, which probably mimic only the hormonal rather than the more important neural actions of endogenous GLP-1.

Evidence supporting the distal intestinal hypothesis derives, in part, from the observation that the bariatric operations most capable of rapidly resolving diabetes—RYGB, BPD, and jejunoileal bypass (JIB) [1,33]—are alike in that they all expedite nutrient delivery to the distal intestine. As predicted from this, they also all enhance GLP-1 secretion [23–25,34]. In the case of JIB, which has been studied the longest, GLP-1 levels increase by up to 10-fold, and elevations in basal and postprandial levels persist for at least 20 years [35,36].

Beyond these correlative data, further support for the distal intestinal hypothesis comes from rodent experiments with ileal interposition. In this procedure, which was initially developed by Koopmans and Sclafani [37], a modest segment of the ileum, with its vascular and nervous supplies intact, is surgically interposed into the proximal small intestine where its exposure to ingested nutrients is greatly increased. As predicted from this anatomy, animals with ileal interposition mount highly exaggerated GLP-1, PYY, and enteroglucagon responses to gastric nutrient loads [38–40]. These hormonal changes are associated with reductions in gastric emptying, food intake, and body weight in the absence of any gastric restriction or malabsorption [38–42]. Interposed rats also display improved glucose homeostasis [39]. This is observed with insulin tolerance tests, suggesting enhanced insulin sensitivity, although the possibility of improved β -cell function has also been noted. Importantly, even in experiments

in which no change in food intake or body weight was observed after ileal interposition, rats with diabetes nevertheless displayed improved glucose tolerance and substantially elevated GLP-1 levels [43]. Very recent work by April Strader and colleagues supports the notion that at least some of the improved glucose homeostasis after ileal interposition is independent of weight loss, and increased GLP-1 is the most obvious candidate to explain this result. Ileal interposition is starting to be explored in humans, and initial reports indicate that it causes substantial weight loss and resolution of diabetes [44].

Despite the cogency and empiric support for the lower intestinal hypothesis, groundbreaking rodent experiments spearheaded by Francesco Rubino demonstrate that additional mechanisms related to the nutrient-excluded proximal intestine, which is a component of RYGB and BPD, can also exert antidiabetic effects. To explore this upper intestinal hypothesis, Rubino developed an operation that leaves the stomach intact but bypasses, with a Roux-en-Y gastrojejunostomy, the same amount of proximal intestine as is circumvented in a standard, conservative RYGB [45]. Although dubbed the “duodenal-jejunal bypass” (DJB), this procedure excludes only a small proportion of the jejunum, and it is primarily a complete duodenal bypass. The operation is essentially a stomach-preserving RYGB that allows investigators to study the effects of circumventing the amount of proximal intestine typical of an RYGB, without the gastric restrictive component.

Rubino et al. [45] initially studied the effects of DJB on Goto-Kakizaki (GK) rats, which are a polygenic nonobese model of type 2 diabetes, developed by selective inbreeding of animals with the highest blood glucose levels. The investigators documented that the amount of bypassed intestine in their DJB is insufficient to cause gross malabsorption, and by design, there is no gastric restriction. Thus, not surprisingly, DJB rats displayed equivalent food intake and body weight to sham-operated controls. Nevertheless, they showed marked improvements in glucose homeostasis, as measured by oral glucose tolerance tests, starting as early as 1 week after the operation and persisting thereafter for 9 months—the equivalent of decades in human life. To confirm that these effects could not result from changes in body weight, the investigators demonstrated that substantial weight loss caused by a draconian low-calorie diet had no impact on glucose tolerance in nonoperated GK rats. The antidiabetic effects of DJB were also considerably more impressive than those achieved with rosiglitazone treatment.

Rubino et al. [46] went on to show in a separate study that DJB normalizes hyperglycemia in fasted and fed *fa/fa* Zucker diabetic fatty (ZDF) rats, which are obese and diabetic due to a mutation in the leptin receptor. This observation is important because it suggests that the beneficial effects of DJB on diabetes may not be unique to the GK rat model. However, unlike GK or wild-type rats, obese ZDF animals displayed reduced food intake and body weight gain after DJB compared with sham-operated controls. Thus, the contribution of upper intestinal bypass per se to their improved glycemia is difficult to distinguish from secondary effects related to body weight.

How could the stomach-preserving DJB ameliorate diabetes in GK rats without causing any changes in food intake or body weight? One possibility is that, similar to some conventional bariatric operations, DJB expedites nutrient delivery to the distal intestine, thereby enhancing L-cell activity and improving glucose homeostasis, for example, through increased GLP-1 secretion. Alternatively, or in addition, antidiabetic effects could result from physiologic alterations related to the exclusion of a short segment of proximal intestine from digestive continuity.

To distinguish between these lower and upper intestinal hypotheses, Rubino et al. [47] performed a variant of their DJB that restored nutrient flow through the previously excluded proximal intestinal segment but retained a gastrojejunostomy at the identical location as in

DJB. In this operation, nutrients from the stomach empty not only into the proximal jejunum but also into the beginning of the duodenum, through the normal pyloric route. The procedure retains the same degree of intestinal shortcutting for nutrients to the distal intestine as with DJB, but it eliminates any physiologic perturbations that might arise from exclusion of the proximal intestine. The results were clear and illuminating. Diabetes was unaffected in GK rats that underwent this gastrojejunostomy operation, in terms of both fasting blood glucose levels and glycemic responses to oral glucose tolerance tests. Furthermore, rats with just a gastrojejunostomy that underwent a second operation to exclude the proximal intestine, creating a DJB, subsequently showed greatly improved glucose tolerance. Conversely, in DJB rats whose diabetes had been ameliorated, the full diabetic GK phenotype was restored if the DJB was converted to just a gastrojejunostomy by reconnecting the stomach with the beginning of the duodenum.

In short, diabetes could be eliminated or restored solely based on the absence or presence, respectively, of nutrient flow through the proximal intestine, with a fixed degree of nutrient shortcutting to the distal intestine. This body of work strongly supports the validity of the upper intestinal hypothesis (i.e., that bypassing a short segment of proximal intestine ameliorates diabetes, independent of effects on food intake, body weight, malabsorption, or nutrient delivery to the distal intestine).

In this issue of *SOARD*, Cohen et al. [12] take the first step toward extending Rubino's rat findings into the clinical arena, reporting 2 cases of persons with diabetes who underwent a DJB. The patients were overweight or mildly obese, with BMIs of 29 and 30.3 kg/m². Their diabetes was not particularly longstanding (2 and 7 years, respectively), and it was treated before surgery with insulin plus metformin in one case, and with rosiglitazone in the other. Although no preoperative laboratory data were shown, evaluations at one week, one month, and thereafter at monthly intervals for 9 months, demonstrated rapid and unequivocal improvements in several simple measures of glucose control. Fasting blood sugars were initially in the diabetic range (148 and 178 mg/dL), but they decreased steadily after surgery, reaching nondiabetic values by 1 month and remaining at <100 mg/dL throughout postoperative months 3 through 9. Similarly, fasting insulin levels started high (27 and 29 mmol/L) but declined quickly and progressively after surgery, remaining at levels typical of persons without diabetes (approximately 5 mmol/L) throughout postoperative months 3 through 9. Reflecting the improvement in glycemia, hemoglobin A1c values fell from diabetic (8%-9%) to normal (5%-6%) values by 3 months, and they remained equally low thereafter during the remaining 6 months of observation. One patient was discharged a few days after surgery without any diabetes medications, and the other had discontinued diabetes medications by 5 weeks after surgery. In short, both patients converted from having poorly controlled diabetes, despite being on diabetes medications, to having normoglycemia off of all such medications. A key finding was that this salutary transformation occurred with no weight loss whatsoever in either patient.

Although conclusions from just 2 cases should be guarded, the data from these individuals are striking. Presuming, for the moment, that similar findings are confirmed in larger studies, they carry several important implications. First, the effect of proximal intestinal bypass to ameliorate diabetes is not unique to rats but extends to humans. Second, the phenomenon generalizes to common obesity-associated type 2 diabetes rather than being a peculiarity of unusual genetic causes of the disease in rodent models (e.g., leptin deficiency in ZDF rats or selective inbreeding of Wistar hyperglycemia-susceptibility genes in GK rats). Finally, and very importantly, the antidiabetic impact of proximal intestinal bypass does not arise simply from increased tolerance to ingested nutrient loads, as one might intuit after a rearrangement of intestinal anatomy, but it also markedly reduces overnight-fasting blood glucose and insulin values. The most impressive results from DJB in previous animal studies were the lowered

glycemic responses to oral glucose tolerance tests, although DJB GK rats, like humans, also showed reductions in fasting blood glucose levels, which converted from diabetic to nondiabetic values after surgery [45]. The ability of this operation to improve both fasting and postprandial glucose levels probably explains its powerful capacity to reduce overall hemoglobin A1c values, at least in the 2 reported patients. In these individuals, the impact of DJB on diabetes was greater than that expected from any extant diabetes medication except insulin, even though the patients lost no weight.

How could exclusion of the upper intestine from digestive continuity ameliorate diabetes without causing weight loss? Candidate mechanisms are not obvious, although we will speculate on a few.

Gastric emptying and upper intestinal motility are almost certainly perturbed after DJB. Theoretically, if the procedure were to slow the delivery of nutrients from the stomach into the small intestine, this effect might lower postprandial glucose excursions, possibly improving overall glycemic control by lessening the maximal demand on β cells. This physiology would be loosely analogous to the effect of α -glucosidase inhibitors, such as acarbose, which improve diabetes control primarily by delaying carbohydrate absorption, leading to lower, broader postprandial glucose peaks. These medications, however, reduce hemoglobin A1c by only approximately 0.5%, whereas A1c levels plunged by $\sim 3.5\%$ in the 2 DJB patients reported by Cohen et al. [12]. In addition, it seems more likely that the exodus of ingesta from the stomach is accelerated after DJB, rather than retarded, because the pylorus may no longer be in a position to restrain gastric outflow. Finally, in both rats and humans, DJB improves not only postprandial glucose levels but also fasting values, and the latter effect is difficult to attribute to a mechanism solely based on altered gastric emptying. Overall, it seems unlikely that changes in upper gastrointestinal motility could account for the antidiabetic effects of DJB.

Rubino et al. [45,47] have proposed that the duodenum produces not only the incretin hormone glucose-dependent insulinotropic polypeptide (GIP) but also an unidentified anti-incretin factor, and they hypothesize that this anti-incretin is hyperactive in the diabetic state. According to their model, the two opposing factors are stimulated by enteral nutrients, so exclusion of the upper intestine from digestive continuity silences both of them. In individuals with diabetes, the result is an improvement in glycemic control, because the putative anti-incretin is said to dominate in this setting. In individuals without diabetes, the opposite situation prevails, and glucose tolerance deteriorates mildly because of a reduction in GIP, which is the more important peptide in the absence of diabetes. This model helps explain Rubino's observation that although DJB lowers blood glucose levels in rats with diabetes, it raises them somewhat in animals without diabetes. Support for the model also derives from a body of literature on the effects of Roux-en-Y intestinal reconstructions after gastrectomy. These reports show that persons with diabetes who undergo operations that exclude the duodenum from nutrient passage enjoy improvement in their disease, despite having lower GIP levels, whereas among individuals without diabetes, glucose tolerance deteriorates mildly after the same operation [48–52].

Although the anti-incretin hypothesis explains certain observations in rats with DJB and humans with gastrectomy, it is difficult to understand why the gastrointestinal tract would produce a nutrient-stimulated factor that impairs insulin secretion and/or action while it simultaneously secretes other factors, such as GLP-1 and GIP, which complement insulin. One teleological hypothesis is that the putative upper intestinal factor that is affected by DJB alters insulin sensitivity in a tissue-specific manner to facilitate proper storage of nutrients in the fed state. By analogy, GLP-1 action in the brain inhibits noninsulin-mediated glucose uptake in muscle, thereby favoring glucose uptake and glycogen formation in the liver, presumably helping fed animals prepare for the next fasted state [53,54]. Whether any similar physiology

pertains to DJB is unknown because it is not clear if this procedure primarily increases insulin secretion, insulin action, or both. Lower insulin levels are observed after the operation, suggesting increased insulin sensitivity, a hypothesis that is also supported by lower glucose nadirs after insulin injections in DJK GK rats [12,45]. However, the reduced glycemia of post-DJB individuals could secondarily increase insulin sensitivity, and the effects of this confounding effect have not yet been excluded. Similarly, it is not known whether circulating insulin levels, although lower in absolute terms after DJB, may be relatively high for a given level of glycemia compared with those in nonoperated controls with diabetes. In short, a detailed analysis of the glycemic phenotype of post-DJB individuals remains to be performed.

Could DJB affect known gut hormones in a manner that would explain its impact on diabetes? Rubino finds in rats that the operation decreases GIP levels, as expected from the postoperative anatomy, and it has little or no impact on GLP-1. Thus, neither of these incretin hormones represents a smoking gun to account for the effects of DJB. In ZDF rats, the procedure corrects a paradoxical postprandial increase that was observed in levels of the orexigenic hormone ghrelin [46]. Because ghrelin exerts many prodiabetic effects, such a change could, theoretically, contribute to the antidiabetic benefits of DJB. Similarly, ghrelin levels typically decrease or are abnormally constrained in the face of massive weight loss after RYGB [20, 21,55], and this alteration could contribute to improvements in diabetes after that operation. Overall, however, data on ghrelin levels after DJB do not clearly support a major role for this hormone in the antidiabetic effects of that procedure. Beyond the few gut hormones that have been studied to date after DJB, the gastrointestinal tract produces more than 100 biologically active peptides [56], and many more could be examined in an attempt to tease out the agents responsible for the beneficial effects of DJB on glucose homeostasis.

Regardless of the mechanisms mediating the antidiabetic actions of DJB, effects of this operation are impressive and very provocative, raising many compelling questions. Would the procedure ameliorate more severe diabetes than that of the 2 patients reported by Cohen et al. [12], who had relatively mild disease? Should DJB or, for that matter, conventional bariatric operations be considered for people with type 2 diabetes who are not sufficiently obese to meet existing criteria for bariatric surgery? Because DJB and several other traditional and experimental gastrointestinal operations are, in fact, increasingly being used throughout the world to treat diabetes, even among people who are not particularly obese, formal recommendations for this type of practice are urgently needed. Hopefully, such guidelines can be established, so that proper clinical trials of “diabetes surgery” can move forward, in tandem with more basic animal experiments designed to elucidate the fascinating mechanisms by which various rearrangements of gastrointestinal anatomy eliminate type 2 diabetes.

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