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Partial ileal bypass affords protection from onset of type 2 diabetes

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Abstract

Background: Partial ileal bypass (PIB) in the National Institutes of Health–sponsored Program on the Surgical Control of the Hyperlipidemias (POSCH) randomized controlled trial was found to reduce plasma cholesterol, in particular low density lipoprotein cholesterol, with concomitant retardation of atherosclerotic cardiovascular disease and increased life expectancy. Glucagon-like peptide-1, related to amelioration of type 2 diabetes, is increased over 5-fold after PIB. We hypothesized that PIB, in addition to its action on cholesterol metabolism, may also prevent type 2 diabetes.

Methods: We surveyed by telephone inquiry of former POSCH patients the 30+ year posttrial incidence of type 2 diabetes or prediabetes, the presence of which was a trial exclusion criteria. We were able to contact 17.4% (n = 838) of the original POSCH population.

Results: Of 66 control responders, 17 contracted type 2 diabetes (25.8%); of 80 PIB responders, 8 contracted type 2 diabetes (10%). The difference between groups was significant ($P = .015$ by Fisher exact test) with an odds ratio of .320 for the PIB group and an over 2-fold (2.6) increase in the incidence of type 2 diabetes in the controls. Including borderline type 2 diabetes (prediabetic) patients, these values were 22 of 66 controls (33.3%) and 10 of 80 PIB patients (12.5%), with an odds ratio of .286 and a $P < .004$, and again an over 2-fold (2.7) increase in the incidence of type 2 diabetes in the control patients.

Conclusion: PIB appears to afford partial protection from the onset of type 2 diabetes for over 30 years. (Surg Obes Relat Dis 2016;▮:00–00.)

Keywords: Type 2 diabetes; 4 partial ileal bypass; POSCH

Partial ileal bypass (PIB) for management of the hyperlipidemias was first clinically performed on May 23, 1963 (Fig. 1) and was the intervention modality in the National Institutes of Health, National Heart Lung and Blood Institute-funded Program on the Surgical Control of the Hyperlipidemias (POSCH) trial [1,2]. By the 1970s, there was a demand for trials to prove that lowering the plasma cholesterol concentration would retard or prevent atherosclerotic coronary artery disease. None of the over 15 published early diet and drug studies were able materially to lower the plasma cholesterol, and were unsuccessful in demonstrating an effect on coronary atherosclerosis [2]. Because the PIB had proven its ability to lower the plasma cholesterol markedly and tolerably, it was proposed, in an investigator-initiated grant application, as an appropriate intervention modality to test the lipid hypothesis in a randomized controlled clinical trial.

The POSCH study was a secondary trial in patients with a documented prior myocardial infarction. The trial compared the

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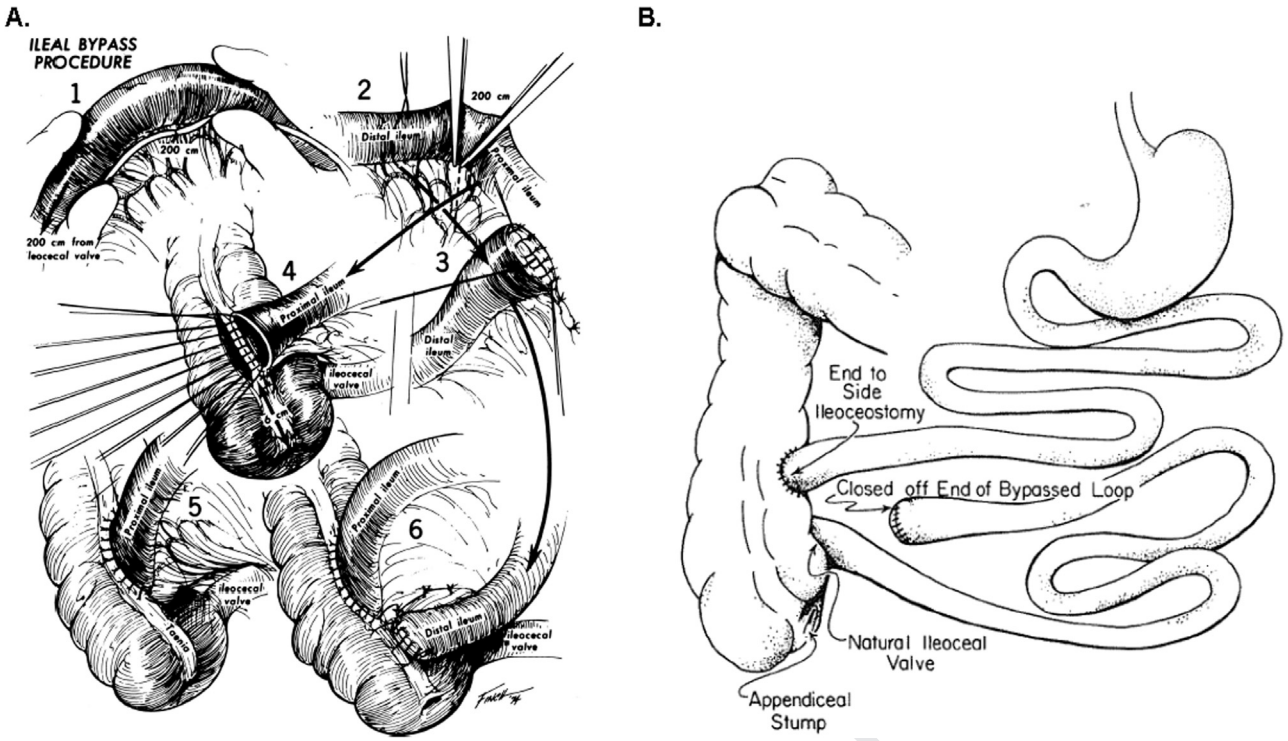

Fig. 1. Partial ileal bypass. A. (1) Measurement of the intestine along the mesenteric border; (2) division of the intestine between marking sutures; (3) closure of distal end of the division; (4) end-to-side anastomosis of the proximal intestine into the anterior taenia of the cecum; (5) completion of anastomosis; and (6) suturing of the closed end of bypassed segment to the anterior taenia and closing of the mesenteric defects. B. Completed partial ileal bypass.

postdietary lipid therapy changes in 421 PIB intervention patients to 417 controls, with a lowering of total plasma cholesterol of 24% ($P < .0001$), a lowering of low-density lipoprotein cholesterol of 38% ($P < .0001$), and an elevation of high-density lipoprotein cholesterol of 4% ($P = .02$). These lipid changes were associated with a 35% ($P < .001$) reduction in the intervention group of death due to coronary heart disease and confirmed recurrent myocardial infarction, as well as a 27% ($P < .038$) reduction in peripheral vascular disease, and a 54% ($P < .005$) diminution in the occurrence of coronary artery surgery or angioplasty. Concurrently with the clinical study, POSCH assessed sequential coronary arteriograms at 0, 3, 5, 7, and 10 years, which found less disease progression in the surgery group, and even statistically significant plaque regression in the PIB cohort [2–4]. POSCH PIB patients exhibited a statistically significant increase in life expectancy; this finding persisted at a 25-year follow-up assessment [5,6].

In the field of metabolic/bariatric surgery, resolution of type 2 diabetes by gastrointestinal tract manipulations was clearly indicated by 1998 [7,8]. In 3 meta-analyses, the procedures that involved shortening of the ileum (biliopancreatic diversion and duodenal switch) were responsible for the highest percentage of type 2 diabetes resolution [9–11]. Recently under evaluation are standard metabolic/bariatric and experimental metabolic operations that will engender type 2 diabetes resolution with minimal or no weight loss in nonobese diabetic patients [12–14].

The gut−diabetes relationship has often been attributed to an increased elaboration of the hormones glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), both secreted by the L-cells of the intestinal mucosa. These hormones seem to work in concert, either eliciting the same metabolic response or augmenting the actions of the other. With respect to pancreatic endocrine function, GLP-1 and PYY contribute to the incretin effect, counteract the insulin depression action of gastrin-stimulating peptide and gastrin-releasing peptide, and stimulate glucose-dependent insulin secretion, preinsulin gene expression, β-cell proliferation, and antiapoptopic pathways [15–19]. It has been found that GLP-1 secretion is reduced in patients with type 2 diabetes [20,21]. In a recent study of the effects of direct human terminal ileum and cecal contact with a food hydrolysate, significant plasma GLP-1 and PYY elevations were found, confirming the ability of the cecum, as well as the ileum, to secrete GLP-1 and PYY on stimulation [22]. In the Goto-Kakizaki rat with naturally occurring type 2 diabetes, ileal bypass or excision did not lower GLP-1 production, but interestingly increased it 5- to 6-fold [23].

These diverse, but possibly complementary, studies gave rise to a hypothesis: The PIB operation, in addition to its action on cholesterol metabolism, may also prevent (and possibly resolve) type 2 diabetes.

Two POSCH trial exclusion criteria were obesity and the presence of diabetes. All of the study's 838 patients were free of type 2 diabetes on randomization. Now, over 30