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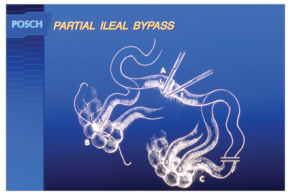
Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

A Perspective: Bariatric Surgery for Obesity and Reversal of Type 2 Diabetes?

Bariatric surgery for the treatment of obesity and the possible reversal of type 2 diabetes is the subject of a personal perspective review by Buchwald and Buchwald (**p. 331**). Benefiting from over 50 years of experience in the area, the authors chart the developments from the very first procedure performed in 1953 through nearly 60 different variations that have been used since then. The authors describe various bariatric and other surgical approaches, and what emerges is a picture of constant flux as surgeons try to find the most effective and safe procedures to help patients. Regarding mechanisms, they highlight that while the approach was developed primarily for weight loss, the metabolic consequences of the procedure are much broader and include the potential reversal of type 2 diabetes. While the procedure undoubtedly results in caloric restriction and nutrient malabsorption, it also appears to affect gut-brain signaling and crucial gut hormones. In the latter case, the authors point out that while the literature is saturated with articles on the topic, it is still not exactly clear how they affect the eating and satiety processes. Focusing on the potential reversal of diabetes, they highlight a key study from 1995 that showed (surprisingly) how Roux-en-Y gastric bypass could normalize blood glucose within 24 h of surgery, effectively ruling out weight loss as the main driver of the subsequent reversal of diabetes. In a key passage they raise the intriguing question of whether learnings from bariatric surgery can be used for an approach that focuses on metabolic outcomes, i.e., true diabetes surgery that is not primarily focused on weight loss or synergistic metabolic medical and surgical avenues of therapy. Commenting further, author Henry Buchwald said: "The primary hoped for outcome of this perspective is for greater cooperation and research by diabetologists, endocrinologists, and basic scientists with metabolic bariatric surgeons to elucidate the neurohormonal mechanisms induced by surgery, and perhaps thereby, the etiologies of obesity and type 2 diabetes."



Partial ileal bypass.

Buchwald and Buchwald. Metabolic (bariatric and nonbariatric) surgery for type 2 diabetes: a personal perspective review. Diabetes Care 2019;42:331–340

A Genetic Risk Score Update to Identify Cases/Risk of Type 1 Diabetes

A genetic risk score called T1D GRS2 can provide improved discrimination between type 1 and type 2 diabetes in adults and can also be highly discriminative in a newborn setting according to Sharp et al. (**p. 200**). The key, according to the authors, is to combine single nucleotide polymorphisms (SNPs) relating to HLA DR-DQ risk (as is currently used), capturing how these markers interact, then adding other SNP data from the HLA region and also a variety of non-HLA SNPs in the wider genome that are tied to type 1 diabetes risk. In all, the approach combines 67 SNPs that are in some way associated with type 1 diabetes risk, identifying more genetic components than previous attempts, especially in the important but difficult to characterize HLA region. They report that the approach was highly discriminative for identifying cases of type 1 diabetes, particularly in younger age-groups. Using a simulation of newborn screening, they suggest their approach was twice as efficient in spotting cases than HLA genotyping (the current approach). The authors indicate that the approach will likely generate major cost savings due to more specific detection, while the possibility of earlier detection may improve the prospects for intervention therapies. While progress with this particular genetic risk score is evident, they do mention potential limitations in terms of general applicability across ethnicities (they only used individuals of European descent) and limitations in coverage and density of the original data—essentially there may still be variants that have not yet been identified that could improve the scoring system even further. Authors William A. Hagopian and Richard A. Oram told *Diabetes Care*: "We expect genetic risk scores like this one based on cost-effective SNPs will become cheap and easy to get. The result will complement immunological and metabolic data for much better overall diabetes prediction."

Sharp et al. Development and standardization of an improved type 1 diabetes genetic risk score for use in newborn screening and incident diagnosis. Diabetes Care 2019;42:200–207

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Longitudinal Pancreas Volume Loss in Type 1 Diabetes

Pancreas volume is reportedly decreased in all stages of type 1 diabetes according to Virostko et al. (**p. 248**). Additionally, it seems that decreases occur in the year following diagnosis, and this loss of volume appears to be accompanied by certain changes in pancreas microstructure. The authors suggest there is likely a previously unknown process involved in the development of type 1 diabetes, particularly from the perspective that loss of β-cell mass would not account for the apparent volume lost in the pancreas. The study involved 51 individuals with recent-onset type 1 diabetes, 57 similarly aged individuals as control subjects, and 20 individuals who did not have diabetes but were positive for more than one autoantibody (indicating risk for type 1 diabetes). Longitudinal MRI measurements were made at baseline, 6 months, and 1 year. The main MRI approach was designed to determine pancreas volume while other protocols were used to determine pancreas tissue microstructure and composition. They found that pancreas volume in the type 1 diabetes cohort was already consistently smaller than pancreas volume in control subjects within 100 days of diagnosis, including when normalized by body weight. The longitudinal measures indicated that in the control subjects, pancreas volume increased in line with growth rates. However, in those with diabetes, pancreas volume declined over the 1-year observation period. Meanwhile, in individuals positive for multiple autoantibodies but without diabetes, pancreas volume was larger than in the diabetes cohort but smaller than in the control subjects. Finally, looking at structure, the authors found a higher apparent diffusion coefficient in the diabetes group, which they suggest indicates loss of cellular structural integrity. Author John Virostko said: "These studies reveal that type 1 diabetes is a progressive whole-organ disease and demonstrate the potential of quantitative MRI to monitor this pancreas pathology. We hope that these MRI tools will prove useful as biomarkers of disease progression and therapeutic response."

Virostko et al. Pancreas volume declines during the first year after diagnosis of type 1 diabetes and exhibits altered diffusion at disease onset. Diabetes Care 2019;42:248–257

Pancreas Volume Reduced in First-Degree Relatives of Individuals With Type 1 Diabetes

First-degree relatives of patients with type 1 diabetes have reduced pancreas volume according research by Campbell-Thompson et al. (**p. 281**). This was in comparison to control subjects who did not have diabetes or autoantibodies associated with the development of diabetes. Specifically, they suggest that first-degree relatives with autoantibodies had even more reduced pancreas volume when compared with autoantibody-negative control subjects or relatives without autoantibodies. The largest degree of reduction in pancreatic size was observed in persons diagnosed with type 1 diabetes within the preceding year. The conclusions come from a cross-sectional study involving first-degree relatives of individuals with type 1 diabetes who were either negative for autoantibodies or positive for a single antibody or multiple autoantibodies. Two further groups were also included as positive and negative control subjects. Pancreas volume was then determined via a specific MRI procedure. As well as determining lower pancreas volume, the authors largely did not find any correlations with measures such as HbA_{1c} or other clinical measures. Concluding, they suggest that pancreas volume, as measured by MRI, might be used as a noninvasive biomarker for predicting risk for type 1 diabetes. According to author Martha L. Campbell-Thompson: "While loss of pancreas size in patients with type 1 diabetes has been known for quite a while, our study is the first to show that relatives of patients with type 1 diabetes have a smaller pancreas size. No one had previously considered that numbers of insulin-producing cells in islets could be at risk due to a smaller pancreas. We are just beginning to study which genes influence pancreas size and how the nonislet cells of the pancreas may communicate with islets to regulate hormone levels. Yet the most striking aspect of our study is that a new biomarker for risk of developing type 1 diabetes was discovered that could be safely measured even in children by a routine clinical radiology test."

Campbell-Thompson et al. Relative pancreas volume is reduced in first-degree relatives of patients with type 1 diabetes. Diabetes Care 2019;42:281–287

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