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In This Issue of *Diabetes*

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Type 1 Diabetes Increases as the pH of Drinking Water Decreases

New data in this issue of *Diabetes* (**p. 632**) suggest that acidic drinking water has a significant effect on gut bacteria leading to higher risk of type 1 diabetes (T1D). Nonobese diabetic (NOD) mice are frequently used as a model for T1D, and previous studies have shown that the composition of gut bacteria in these mice influences the incidence of T1D. It had been widely assumed that differences in laboratory and colony cleanliness were primary factors that lead to differences in gut microflora and ultimately to differences in T1D incidence. However, dietary factors that influence the makeup of the gut microbiome might also explain differences in T1D in this mouse model. In the new work presented here, Sofi et al. explore the possibility that the pH of drinking water impacts the gut microbiome and, in turn, T1D. Female NOD mice were maintained in pathogen-free facilities and were given autoclaved neutral (pH 7.0–7.2) water (NW) or acidic water (AW) with added HCl (pH 3.0–3.2). Mice purchased at 3–4 weeks that had been given AW since birth were continued on AW or switched to NW. The group that continued on AW developed hyperglycemia rapidly compared with the group switched to NW. In contrast, prediabetic mice purchased at 8 weeks and continued on AW did not show a difference in disease progression compared to those switched to NW. In-house NOD mice that were given AW exhibited faster onset and progression of T1D, similar to the mice purchased at 3–4 weeks. However, in-house NOD mice that were given NW showed slower disease progression. Notably, fecal transfer using pellets positive for segmented filamentous bacteria, a common mouse pathogenic bacteria known to affect autoimmune outcomes, decreased the incidence of T1D in mice on AW but not those on NW. Although AW and NW mice had similar gut microflora densities, AW mice exhibited less diversity. Together, these results suggest that the direct impact of the pH of drinking water on diabetes risk may be less important than the indirect impact of pH on the gut microbiome. — *Laura Gehl, PhD*

Sofi et al. pH of drinking water influences the composition of gut microbiome and type 1 diabetes incidence. Diabetes 2014;63:632–644

GLP-1 Receptor Agonist Sensitivity Predicts Success of Gastric Bypass in Rats

New research shows that sensitivity to glucagon-like peptide 1 (GLP-1) receptor (GLP-1R) agonism predicts glucose tolerance after gastric bypass. In most patients, Roux-en-Y gastric bypass (RYGB) decreases body weight (BW) by approximately 60–70% while increasing glucose tolerance. This procedure is also associated with increased levels of GLP-1. In this issue of *Diabetes*, Habegger et al. (**p. 505**) hypothesize that responsiveness to GLP-1R agonists could predict the degree of metabolic benefit resulting from RYGB. In a novel series of experiments, diet-induced obese (DIO) male rats were first administered the GLP-1R agonist exendin-4 for 4 days. The animals were evaluated for GLP-1R agonist sensitivity using measures of BW, food intake, and ad libitum blood glucose measurements, as well as their response to a GLP-1 challenge during an intraperitoneal glucose tolerance test. The 25 most responsive and 25 least responsive rats were identified from the original pool of 197, and these were subjected to RYGB surgery and followed for 130 days. Ten rats with intermediate GLP-1R responsiveness served as controls by administration of a sham surgery. As expected, RYGB caused a decrease in BW in both the responder and nonresponder groups compared with the control animals. However, the responder group exhibited enhanced glucose tolerance 3 months after RYGB compared with nonresponders, an observation that was independent of BW or fat mass. Because these findings suggest that GLP-1R agonist sensitivity predicts glucose metabolism after RYGB, the investigators propose that using GLP-1R agonism as a biomarker may allow clinicians to optimize the use of RYGB, thereby enhancing efforts to tailor the treatment of type 2 diabetes. — *Laura Gehl, PhD*

Habegger et al. GLP-1R responsiveness predicts individual gastric bypass efficacy on glucose tolerance in rats. Diabetes 2014;63:505–513

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Closely Related Coxsackievirus Serotypes May Have Opposing Effects on Risk of Type 1 Diabetes

An article in this issue of *Diabetes* (**p. 446**) suggests that coxsackievirus B1 (CVB1) may be associated with an increased risk of type 1 diabetes (T1D). For some time, enteroviruses have been considered possible environmental triggers of T1D. More than 100 different enterovirus serotypes are known, and they cause a variety of diseases by attacking diverse cell types and organs. Laitinen et al. present new findings related to specific enterovirus serotypes that may differentially influence the risk of T1D. Using a population derived from the Diabetes Prediction and Prevention (DIPP) study in Finland, investigators selected 183 case children, who were either persistently positive for two or more diabetes autoantibodies or who had progressed to clinical T1D, and 366 matched control children. Importantly, all DIPP children were at increased risk for T1D based on cord-blood HLA typing. Neutralizing antibodies were measured in serum or plasma against 41 enterovirus serotypes. Although CVB serotypes 1, 3, and 6 are genetically very similar, CVB3 and CVB6 were less common in case children than in control children, while CVB1 was associated with an increased risk of β-cell autoimmunity. These findings suggested that the closely related CVB serotypes were associated with differential risk of T1D. Although results showed that CVB1 infections reached peak levels several months before autoantibodies first appeared, children infected with CVB1 and one of the protective serotypes showed a decreased risk of developing T1D, an observation suggesting a biological interaction between the two serotypes with regard to diabetes risk. These results confirm previous findings suggesting that enterovirus infections may influence the onset of T1D, and they offer new insight into the individual and joint risks associated with CVB infections. The new work reported in this issue suggests that the development of an enterovirus vaccine for the prevention of T1D may warrant future exploration. — *Wendy Chou, PhD*

Laitinen et al. Coxsackievirus B1 is associated with induction of β-cell autoimmunity that portends type 1 diabetes. Diabetes 2014;63:446–455

GLP-1 Pathway Implicated in Insulin Secretory Response to LPS

Abundant in the gut, bacterial endotoxins have inflammatory effects that cause metabolic derangements, including hyperglycemia. In this issue of *Diabetes*, new work by Nguyen et al. (**p. 471**) focuses on the responses of mice to induced hyperglycemia and exposure to *E. coli*–derived lipopolysaccharides (LPS). The new findings show that relative to controls, both glucose clearance and glucose-stimulated insulin secretion (GSIS) were significantly enhanced in mice that received acute LPS injections. Other mice received several weeks of continuous LPS infusion that simulated the effects of a high-fat diet, and these mice also demonstrated elevated glucose disposal and GSIS. The article provides several lines of evidence for a molecular mechanism for LPS-triggered increased insulin secretion involving the glucagon-like peptide 1 (GLP-1) pathway. The investigators showed that LPS treatment plus administration of sitagliptin (a DPP-4 blocker) resulted in both an augmented GSIS response and improved glucose clearance. Conversely, they observed that the use of a GLP-1 antagonist muted LPS-mediated changes in glucose metabolism. Experiments involving GLP-1 receptor knockout mice indicated no GSIS increase in these mice following LPS treatment, an observation that further supports a role for the GLP-1 pathway. This new work has potentially far-reaching clinical implications because it highlights endotoxemia as a significant inducer of insulin secretion and acknowledges the important role of GLP-1 as a target for LPS. — *Wendy Chou, PhD*

Nguyen et al. Lipopolysaccharides-mediated increase in glucose-stimulated insulin secretion: Involvement of the GLP-1 pathway. Diabetes 2014;63:471–482

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