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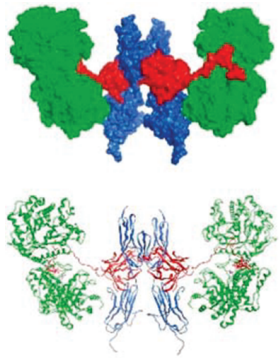
In This Issue of *Diabetes*

By Max Bingham, PhD

FGF19 Analog Replicates Liver Outcomes of Bariatric Surgery

Fibroblast growth factor 19 (FGF19) is a gut hormone that circulates in the bloodstream to regulate metabolism, and according to DePaoli et al. (**p. 1315**), an analog of it appears to faithfully replicate one of the major benefits of bariatric surgery. Using a series of mouse models, the authors show that FGF19 can have strong glucose-lowering effects but that safety concerns (mainly carcinogenesis) would probably limit the approach. To solve this, they use a complex in vivo screening approach to identify FGF19 analogs that could reduce glucose but not generate tumors in *db/db* mice. The eventual result, according to the authors, was NGM282, which they then tested in a randomized controlled trial. Briefly, they tested the effects of three doses of the analog plus controls over 28 days in 81 individuals with type 2 diabetes. The primary outcome was absolute change in fasting plasma glucose over the study period. However, none of the tested doses resulted in significant glucose changes, in complete contrast to the glucose-lowering effects seen in the animal models. However, they did find potent effects of the analog at all doses on markers of nonalcoholic steatohepatitis (NASH). They go on to describe additional experiments in further murine models to explore the effects in more detail. Based on the outcomes, they suggest that with more studies, it might be the case that the FGF19 analog combined with a GLP-1 analog could be the sought-after combination of factors that can deliver the benefits of bariatric surgery—without the surgery. Author Lei Ling commented: "The improbable emergence of bariatric surgery as an accepted treatment for diabetes has inspired researchers to uncover the underlying mechanisms of the procedure. Although the FGF19 analog NGM282, a 'designer hormone,' did not correct hyperglycemia in the clinic, it has demonstrated powerful benefits to liver health, including marked improvements in liver fat and histology, and may provide a noninvasive alternative to bariatric surgery in patients with NASH."



An unbiased, systematic, in vivo screen of FGF19 mutants in diabetic *db/db* mice. Molecular modeling of the FGF19-βKlotho-FGFR1 2:2:2 ternary complex. βKlotho is in green, FGF19 in red, and FGFR in blue. Ribbon structure of the same complex is shown in the bottom panel.

DePaoli et al. FGF19 analog as a surgical factor mimetic that contributes to metabolic effects beyond glucose homeostasis. Diabetes 2019;68:1315–1328

Anti-Thymocyte Globulin Therapy Preserves β-Cell Function in Type 1 Diabetes

The TrialNet consortium provides an update on their investigation into low-dose anti-thymocyte globulin (ATG) and the potential it might have in delaying type 1 diabetes progression. According to Haller et al. (**p. 1267**), at the 2-year progression point in the trial, they found that patients treated with ATG alone continued to have higher C-peptide levels versus those treated with placebo (an indication that β-cells were still working) and that HbA_{1c} levels continued to remain lower than that of controls. The study involved 89 individuals with type 1 diabetes who originally received infusions of ATG alone, ATG plus granulocyte colony-stimulating factor (GCSF), or placebo. Blood samples were then collected at regular study visits to establish C-peptide levels and HbA_{1c} as well as for mechanistic studies. They found that C-peptide was significantly higher in individuals who received ATG alone (versus placebo). In contrast, the combination of ATG and GCSF did not result in C-peptide levels that were different from placebo. Both treatments also resulted in decreases in HbA_{1c}, and there was no difference in insulin use between the groups. In terms of the mechanistic studies, they uncovered a number of alterations in immune markers that occurred in the treatment groups. These included reduced CD4:CD8 ratio, an increase in the ratio between regulatory T cells and conventional CD4 T cells, and an increase $PD\text{-}1^{+}CD4^{+}$ T cells. They suggest that the patterns uncovered might help explain the apparent maintenance of β-cells due to the ATG treatment. Author Michael J. Haller told *Diabetes*: "Low-dose ATG preserved C-peptide and reduced HbA_{1c} for at least 2 years in people with new-onset type 1 diabetes. The ability to safely and effectively repurpose an immunotherapy like ATG highlights ongoing progress towards our ultimate goal of preventing and reversing the disease. Looking to the immediate future, low-dose ATG, both as a monotherapy and in combination with other agents, should be considered as a potential means for preventing type 1 diabetes and preserving β-cell function in type 1 diabetes."

Haller et al. Low-dose anti-thymocyte globulin preserves C-peptide, reduces HbA_{1c}, and increases regulatory to conventional T-cell ratios in new-onset type 1 diabetes: two-year clinical trial data. Diabetes 2019;68:1267–1276

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Surgical Denervation of the Common Hepatic Artery: Type 2 Diabetes Treatment Option?

Surgical sympathetic denervation of the common hepatic artery improves glucose tolerance in dogs fed a high-fat high-fructose diet according to Kraft et al. (**p. 1143**). Specifically, the approach seems to improve glucose tolerance by ~60% and likely involves improved β-cell function and also improved insulin and glucose action in the liver. While much more work will be needed, the authors suggest that the approach might be useful as a therapy for improving glucose tolerance in type 2 diabetes. The conclusions are the result of a study with dogs who were administered an oral glucose tolerance test at baseline and then fed a diet high in fat and fructose for 4 weeks. The animals were then randomized to receive either surgical sympathetic denervation of the common hepatic artery or a sham operation. Further oral glucose tests were then administered in the coming weeks, with some animals receiving a test at 3 months postsurgery. A subset of dogs also underwent hyperinsulinemic-hyperglycemic clamp testing to establish whether hepatic glucose metabolism improvements were independent of insulin release. The authors found that compared to dogs on a standard diet, dogs fed with the test diet had a marked increase in plasma glucose and livers incapable of taking up glucose but that surgery reduced the abnormalities in glucose tolerance by as much as 60%. Sham surgery, meanwhile, led to no such improvements. Additional measurements then indicated that insulin action and glucose tolerance were enhanced. The authors go on to explain mechanisms that might be involved, focusing mainly on the consequences of reducing the sympathetic innervation of the liver but also in wider anatomical structures including the pancreas. They ultimately conclude that stripping of the nerves lessens some of the metabolic defects and results in increasing glucose tolerance.

Kraft et al. Sympathetic denervation of the common hepatic artery lessens glucose intolerance in the fat- and fructose-fed dog. Diabetes 2019;68:1143–1155

Hyperuricemia Linked to Obesity but Not Insulin Resistance or Dyslipidemia

Hyperuricemia positively correlates with obesity and the allied metabolic disruption but is not likely to be causative, according to Harmon et al. (**p. 1221**). Specifically, in mice, either genetic deletions or pharmacological inhibition of xanthine oxidoreductase resulted in reduced plasma uric acid levels and thus hyperuricemia. However, neither approach resulted in improved insulin resistance or dyslipidemia, essentially ruling out hyperuricemia as a cause of metabolic disruption in obesity. The findings are the result of a series of experiments with mice that had a hepatocyte-specific knockout of *Xdh*, which is the gene that encodes xanthine oxidoreductase, the sole source of uric acid. Additional experiments also included pharmacological inhibition of xanthine oxidoreductase with febuxostat. Both approaches also assessed the effects of reducing or preventing hyperuricemia on metabolic outcomes in obesity. The authors found that the *Xdh* knockout did substantially lower *Xdh* expression and xanthine oxidoreductase activity in plasma and reduced liver and plasma uric acid levels in comparison to controls. When exposed to obesity via diet, both the mice with the knockout and controls became obese, but there was no hyperuricemia present in the knockout mice. Nevertheless, both sets of mice developed insulin resistance and dyslipidemia, suggesting that hyperuricemia associated with obesity is not contributing to insulin resistance. Confirming the observations, the authors also found that febuxostat could lower plasma and tissue uric acid levels as well as xanthine oxidoreductase activity in obese wild-type mice, but this had no effect on insulin resistance or dyslipidemia. The link between hyperuricemia and obesity has led to wide speculation that it might explain associated metabolic outcomes, including insulin resistance. However, as the authors note, previous investigations have produced inconsistent results due to a combination of a lack of focus on metabolic outcomes, imprecise measurements, data interpretation issues, and inappropriate animal models. They note that their approach should address these concerns.

Harmon et al. Hepatocyte-specific ablation or whole-body inhibition of xanthine oxidoreductase in mice corrects obesity-induced systemic hyperuricemia without improving metabolic abnormalities. Diabetes 2019;68:1221–1229

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