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In This Issue of *Diabetes Care*

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Genetic Predictors of Cardiovascular Mortality During Intensive Glycemic Therapy: New ACCORD Trial Data

Two genetic variations may act as potential determinants of the increased cardiovascular mortality that was seen in the intensive treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial—reopening a debate on precisely what caused the increased mortality, but at the same time offering a potential second chance to the controversial therapy. According to Shah et al. (**p. 1915**), the genetic variants were identified in a genome-wide association study into cardiovascular mortality in the intensive treatment arm of ACCORD. Out of nearly 7 million common variants that were screened, two variants reached genome-wide significance. Both were associated with increased risk of cardiovascular death in the intensive treatment arm but not in the standard treatment arm. When combined into a so-called genetic risk score (GRS), participants with a score of zero experienced reduced risk of cardiovascular mortality, a score of one translated to no difference in risk, and a score of two or more translated to significantly increased risk. By their very nature, genome-wide association studies can throw up spurious results, so to try to validate their findings the authors also examined patients with type 2 diabetes in two other long-term studies and found that GRS also modulated the association between glycemic control and cardiovascular mortality in the same way as in ACCORD. According to the authors, the outcomes suggest that the two variants might be used to predict how a patient might fare in terms of cardiovascular mortality risk if they were to receive intensive glycemic treatment. The outcomes also suggest that the two variants might hint toward as yet undescribed pathways at play that link glucose metabolism and cardiovascular outcomes. Commenting more widely on the significance of the study, author Alessandro Doria told *Diabetes Care*: "We are quite excited about these findings as they shed some light on the great paradox of increased cardiac mortality seen in ACCORD. These variants require further validation, but they do have the potential to provide a cheap and effective precision medicine tool to revive intensive glucose control as a therapy to prevent cardiovascular complications in type 2 diabetes."

Shah et al. Genetic predictors of cardiovascular mortality during intensive glycemic control in type 2 diabetes: findings from the ACCORD clinical trial. Diabetes Care 2016;39:1915–1924

Metformin and Sitagliptin May Maintain Remission From Hyperglycemia in Obese African American Patients

More than half of African Americans who present with new-onset diabetic ketoacidosis (DKA) are obese. With intensive insulin treatment, many of these patients achieve near-normoglycemia remission, which is defined as the ability to stop insulin and maintain good glycemic control. The period of near-normoglycemia remission is variable. According to the results of a randomized controlled trial by Vellanki et al. (**p. 1948**), both metformin and sitagliptin may help prevent hyperglycemic relapse following remission after insulin treatment in these patients. The small study (n = 48) had a prospective, 4-year, placebo-controlled, randomized design that assigned subjects to either metformin, sitagliptin, or placebo after they had been treated with intensive insulin to achieve normoglycemia. Subsequently, the patients were followed with oral glucose tolerance tests at randomization and at 3 months and after that every 6 months to check glycemic levels and various measures of insulin sensitivity and β-cell function. Both metformin and sitagliptin treatments resulted in significantly longer periods without hyperglycemic relapse than placebo. The authors report that the subjects taking either metformin or sitagliptin were ~70% less likely to experience hyperglycemic relapse. Their subsequent analyses of insulin sensitivity parameters reportedly suggest that this prolonging of near-normoglycemia levels was likely due to improvements in insulin secretion rather than changes in insulin sensitivity. Based on their analysis, they suggest that subjects that did experience a relapse to hyperglycemia had lower insulin secretion. In conclusion, the authors suggest that both metformin and sitagliptin can be used to prolong normal glycemic levels and remission from hyperglycemia following insulin treatment in these patients. Commenting more widely on the study, author Priyathama Vellanki stated: "While we do not know the exact prevalence of obese African Americans who present with DKA who achieve normoglycemia, prolongation of remission may change the clinical course and prevent long-term diabetic complications for a large number of African American patients with diabetes."

Vellanki et al. Randomized controlled study of metformin and sitagliptin on long-term normoglycemia remission in African American patients with hyperglycemic crises. Diabetes Care 2016;39:1948–1955

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A Combination of Insulin Glargine and Lixisenatide Proves More Effective Than Its Components for Controlling Glycemia in Type 2 Diabetes

LixiLan, an insulin glargine/lixisenatide combination, is likely more effective at achieving improvements in glycemic control than when its component parts are given alone, according to the outcomes of the LixiLan-O (Efficacy and Safety of Insulin Glargine/Lixisenatide Fixed Ratio Combination Compared to Insulin Glargine Alone and Lixisenatide Alone on Top of Metform in Patients with T2DM) study. Reportedly, the combination could achieve near normal glycemia levels in patients with poorly controlled type 2 diabetes and at the same time achieve this without increases in either hypoglycemia, weight, or exceptional gastrointestinal adverse events. The large, multicenter, randomized phase III trial primarily examined the effects of either the combination or its components on HbA_{1c} over 30 weeks of intervention in patients with type 2 diabetes. Secondary outcomes included effects on plasma glucose, body weight, percentages of patients reaching a range of HbA_{1c} targets, hypoglycemia, and a range of safety end points. According to Rosenstock et al. (**p. 2026**), the combination LixiLan group reached a mean final HbA_{1c} of 6.5%, while the groups on insulin glargine or lixisenatide alone reached 6.8 and 7.3%, respectively. Many more subjects reached the HbA_{1c} targets in the combination group than in the other component groups. Mean body weight decreased in the LixiLan and lixisenatide groups but increased in the insulin glargine group. The overall safety profile suggested hypoglycemia occurred at a similar rate in the LixiLan and lixisenatide groups and at a lower rate in the insulin glargine group. Gastrointestinal events in the LixiLan group were lower than in the lixisenatide group (a persistent issue with the glucagon-like peptide 1 receptor agonist drugs is gastrointestinal adverse events). Taken together, these results suggest the combination gives meaningful reductions in HbA_{1c} while addressing many of the concerns associated with taking the components alone (i.e., weight gain with insulin and gastrointestinal events with lixisenatide). They also suggest that combining drugs into treatments for glycemic control should be considered more widely as it seems the approach takes advantage of the complementary actions of each drug while at the same time mitigating potential adverse events.

Rosenstock et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care 2016;39:2026–2035

Genetic Variant of Fibroblast Growth Factor 21 Modifies Outcomes of Weight-Loss Diets

Dietary interventions that modify macronutrient intakes can be used to control body weight and fat distribution, particularly in the case of overweight or obesity. However, interindividual responses to such interventions can be considerable. A study by Heianza et al. (**p. 1909**) suggests that a specific variant in the fibroblast growth factor 21 (*FGF21*) gene may interact with carbohydrate/fat intake and result in variations of outcomes relating to central adiposity and body fat composition. According to the authors, as a result it should be possible to provide more precise dietary interventions that consider this genotype. The study examined 715 overweight or obese individuals. These individuals were part of the Preventing Overweight Using Novel Dietary Strategies (POUNDS) Lost trial. They were examined by genotyping the *FGF21* gene and also assessing their body composition. The individuals were also assigned to one of four diets that varied in fat, protein, and carbohydrate and then were followed up over a period of two years. Individuals with the CC genotype of *FGF21* lost more fat and had reduced waistlines at two years but only after following a high-carbohydrate/low-fat reduced-calorie diet. The opposite was largely the case on a high-fat/low-carbohydrate reduced-calorie diet (i.e., they lost less fat or had less reduced waistlines). In comparison, individuals with the TT variant lost the most on the high-fat/low-carbohydrate diet and the least on the low-fat/high-carbohydrate diet. Individuals with the mixed TC variant consistently had outcomes in between. According to the authors, their findings are largely in line with the known biological roles of *FGF21*, which in general terms is thought to be involved in both glucose and fat metabolism. However, as they report, there is still much that is unknown about *FGF21*. Nevertheless, they go on to suggest that it may represent a target for treating obesity and that based on genotype, it might be possible to offer more specific dietary advice to patients who need to lose weight. Commenting more widely on the study, author Lu Qi said: "Growing evidence from observational studies and randomized clinical trials suggests the potentially important role of genetic variation in affecting interindividual responses to diet and lifestyle interventions. More comprehensive and in-depth investigations on gene–diet and gene–lifestyle interactions are urgently needed to provide support to precision prevention in the future."

Heianza et al. Macronutrient intake–associated *FGF21* genotype modifies effects of weight-loss diets on 2-year changes of central adiposity and body composition: the POUNDS Lost trial. Diabetes Care 2016;39:1909–1914

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