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Diabetes Care®

In This Issue of *Diabetes Care*

Edited by Helaine E. Resnick, PhD, MPH

Prospective Link Between Hypoglycemia and Macrovascular Events

A report in this issue of *Diabetes Care* (**p. 3301**) adds to the evidence base supporting an association between hypoglycemia and risk of macrovascular events. The new study is based on prospective data from more than 1,000 adults with type 2 diabetes who were between the ages of 60 and 75 years at baseline. The clinical profiles of these participants were characterized in detail, including baseline levels of inflammatory markers and history of hypoglycemic episodes. After 4 years of follow-up, investigators found that relative to participants with no history of severe hypoglycemia, the odds of macrovascular events, coronary heart events, and myocardial infarction were 2.1, 2.4, and 4 times higher among those who reported a history of one or more hypoglycemic episodes. In addition to their increased risk of clinical events, participants who experienced hypoglycemia had significantly higher measures of four inflammatory markers—CRP, fibrinogen, IL-6, and TNF-α—an observation suggesting a potential mediating role for these markers in the association between hypoglycemia and macrovascular end points. However, when the inflammatory markers were entered into multivariate models, the association between hypoglycemia and vascular end points persisted, indicating that the markers did not mediate this relationship. Although the authors point out that the study is limited by the relatively short follow-up period, the modest number of incident events, and the fact that the inflammatory markers were not measured at the same time as hypoglycemic episodes, they also emphasize the large sample size, limited loss to follow-up, and the diversity of the diabetic patient population. Against the highly publicized backdrop of mixed findings from large clinical trials of aggressive glucose control in diabetes, the observations from this new report suggest that there may be benefits associated with giving added attention to defining ideal glycemic targets, especially in older adults and others who may be at risk for hypoglycemia. — *Helaine E. Resnick, PhD, MPH*

Bedenis et al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh Type 2 Diabetes Study. Diabetes Care 2014;37:3301–3308

Diabetes Remission Is Extremely Rare

A study published in this issue of *Diabetes Care* (**p. 3188**) demonstrates that diabetes remission—as defined by a 2009 American Diabetes Association consensus panel—is quite rare in the absence of bariatric surgery. The new study, which is based on the information from nearly 123,000 insured adults, quantified diabetes remission over 7 years and highlights findings for partial, complete, and prolonged remission in this large community-based cohort. The 7-year cumulative incidence of any category of remission was 1.60%, and the incidence of partial, complete, and prolonged remission was 1.47%, 0.14%, and 0.007%, respectively. Although several demographic factors including older age, lower baseline HbA_{1c}, and <2 years of diabetes since the time of diagnosis were associated with greater likelihood of remission, the authors also pointed out that in 2006, the likelihood of someone in this cohort dying was more than twice that of having diabetes remission. Despite this discouraging observation, results of the new study challenge the long-held belief that diabetes is irreversible. Given the prevailing wisdom concerning the benefits of aggressive glucose control, the authors provide a detailed discussion on the differences between their findings and those from the Look AHEAD study that achieved a remission rate of 11.5% in the intensive management arm. Results from Look AHEAD, which enrolled diabetic patients who were motivated to make meaningful lifestyle changes, contrasted sharply with findings from diabetic individuals in the community-based sample in the new report. The marked differences in remission in the two samples may provide a platform for discussion of how to assess readiness for change among diabetic patients and how to appropriately manage diabetes among various patient subgroups. — *Helaine E. Resnick, PhD, MPH*

Karter et al. Incidence of remission in adults with type 2 diabetes: the Diabetes & Aging Study. Diabetes Care 2014;37:3188–3195

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Gradient Effects of Antepartum Glucose Measures on Postpartum Glucose Regulation

Intriguing findings in this issue of *Diabetes Care* (**p. 3262**) show a stepwise impact of antepartum glucose measures on postpartum β-cell function and insulin sensitivity. The new research is based on data from 337 women who had glucose challenge testing (GCT) and oral glucose tolerance testing (OGTT) in pregnancy, followed by OGTTs at 3 months, 1 year, and 3 years postpartum. The women were categorized into four groups based on their gestational glucose tolerance testing: gestational diabetes mellitus (GDM), gestational impaired glucose tolerance, abnormal GCT with normal glucose tolerance (NGT) on the OGTT, and normal GCT with NGT. Data from the postpartum OGTTs were used to derive indices of β-cell function, insulin sensitivity, and measures of fasting and 2-h glucose. The four gestational glucose groups were then examined in relation to the postpartum glycemic outcomes at each point in time. The data showed that categories of antepartum glucose groups were associated with a stepwise gradient of unfavorable glucose regulation at each of the three postpartum time points. More striking was the observation that the categories of antepartum glucose regulation predicted distinct trajectories of postpartum glucose dysregulation. For example, women with GDM had an upward trajectory of 2-h glucose over time while the other groups' measures were relatively constant. Other observations included the finding that although all groups had declining insulin sensitivity over time, they remained on parallel trajectories during the follow-up period. These data, which demonstrate the heterogeneity of prospective relationships between antepartum and postpartum glucose regulation measures, may not only help clinicians better assess postpartum diabetes risk but may also facilitate provision of tailored interventions that meet the needs of women with specific antepartum glucose profiles. — *Helaine E. Resnick, PhD, MPH*

Kramer et al. Each degree of glucose intolerance in pregnancy predicts distinct trajectories of β-cell function, insulin sensitivity, and glycemia in the first 3 years postpartum. Diabetes Care 2014;37:3262–3269

Novel Methods Isolate Liraglutide's Impact on β-Cell Function

New data in this issue of *Diabetes Care* (**p. 3270**) demonstrate the favorable impact of liraglutide on β-cell function and show that this effect is independent of baseline glucotoxicity. In type 2 diabetes, β-cell dysfunction is believed to result from a combination of β-cell destruction and glucotoxicity—the unfavorable impact of glucose on β-cell function. Clinical trials that do not account for the impact of baseline glucotoxicity may not accurately assess the impact of a new medication, and this methodological issue also has important implications for studies that seek to distinguish a drug's impact on glucotoxicity from its impact on β-cell preservation. Short-term intensive insulin therapy (IIT) has been proposed as a strategy to eliminate glucotoxicity before randomization, and this approach was used in the newly published report. Fifty-one type 2 diabetic patients with an average HbA_{1c} of 6.8% at baseline were followed for 48 weeks with a focus on the insulin secretion–sensitivity index as the primary end point. To address baseline glucotoxicity, participants were given IIT for 4 weeks before randomization, at which point one group received injected liraglutide and the other received a sham injection. Although results demonstrated that liraglutide markedly enhanced β-cell function relative to placebo with no increase in hypoglycemia or other adverse events, the benefit was completely lost within 2 weeks after stopping the drug. However, the authors emphasized that although the drug performed well in terms of β-cell function and safety, it did not impact factors that promote β-cell destruction, mechanisms that many consider to be crucial targets for development of future therapies. — *Helaine E. Resnick, PhD, MPH*

Retnakaran et al. Liraglutide and the preservation of pancreatic β-cell function in early type 2 diabetes: the LIBRA trial. Diabetes Care 2014;37:3270–3278

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