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In This Issue of *Diabetes Care*

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Glucose Peaks in Diabetes Linked to Declines in Cognitive Function and Dementia

Long-term decline in cognitive function and the development of dementia has long been associated with diabetes. Indeed, the risk of dementia and cognitive decline increases with raised levels of average blood glucose (i.e., HbA_{1c}) according to many studies. And yet, HbA_{1c} might not capture some aspects of glycemia that might be highly relevant to cognitive decline. One of these, glycemic peaks, has now been identified as an independent risk factor for cognitive decline and dementia in diabetes. According to Rawlings et al. (**p. 879**) who report the link, targeting glucose peaks may be crucial for the prevention of cognitive decline in diabetes patients. The study examined nearly 13,000 people involved in the Atherosclerosis Risk in Communities (ARIC) study for cognitive decline and dementia in a series of visits over a period of ~20 years. The researchers also established average blood glucose (via HbA_{1c}) and glucose peaks (via 1,5-anhydroglucitol [1,5-AG], a marker of glucose peaks). According to the authors, just over 1,100 participants developed dementia in the follow-up period. Of those that had concurrent diabetes, each 5 µg/mL decrease in 1,5-AG (thus glucose peaks) increased the risk of dementia by 16%. They identified a trend toward greater cognitive decline in those with diabetes and HbA_{1c} <7%. However, among participants with diabetes and HbA_{1c} >7%, cognitive decline was greater overall when glucose peaks were present versus when they were not. The relationship also reached statistical significance after accounting for a long list of potential confounding factors, leading the authors to conclude that glucose peaks, on top of average glycemia, are a risk factor in diabetes for cognitive decline and dementia. Commenting more widely on the study, author Elizabeth Selvin told *Diabetes Care*: "Our results suggest that in persons with diabetes, glycemic variability may be important above and beyond average glucose. This means that controlling swings in glucose may be helpful for improving health outcomes including cognitive health."

Rawlings et al. Glucose peaks and the risk of dementia and 20-year cognitive decline. Diabetes Care 2017;40:879–886

Specific Metabolic Profiles Associated With Maternal BMI and Glycemia Translate to Diabetes Risk in Children

Two metabolic profiling analyses by Lowe et al. (**p. 902**) and Jacob et al. (**p. 911**) suggest there are specific metabolic signatures associated with maternal BMI and glycemia and that these in turn are associated with different components of the newborn metabolome that may determine newborn size at birth. More specifically, maternal BMI is likely associated with a newborn metabolome that is reportedly characteristic of insulin resistance and type 2 diabetes risk. The conclusions come from further analyses of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study and involved targeted metabolomic assays of blood samples obtained from mothers with a variety of ancestry backgrounds at ~28 weeks of gestation and umbilical cord blood at the subsequent birth event. The initial analysis by Jacob et al. revealed an array of metabolites relating to glycemia that appear enriched with gluconeogenic substrates while BMI appears to be associated with a number of lipid-related metabolites. It also suggests that pregnancy-induced insulin resistance might, in some cases, be associated with metabolic features that are indicative of maternal mitochondrial dysfunction. The question then arises as to whether these metabolic changes impact on pregnancy outcomes and according to the article by Lowe et al., it likely does. They report that overall, cord metabolites at birth largely correlate with maternal levels of the same metabolites at 28 weeks of gestation. In turn, some of these correlated with newborn birth weight and a measure of adiposity. The authors significantly suggest that the combination of metabolites in some cases are indicative of insulin resistance and the risk of type 2 diabetes. According to author William L. Lowe Jr.: "The BMI- and glycemia-induced changes that we observe in the fetal metabolome are intriguing. The challenge going forward is to determine the mechanism by which these changes contribute to fetal outcomes."

Lowe et al. Maternal BMI and glycemia impact the fetal metabolome. Diabetes Care 2017;40:902–910

Jacob et al. Targeted metabolomics demonstrate distinct and overlapping maternal metabolites associated with BMI, glucose, and insulin sensitivity during pregnancy across four ancestry groups. Diabetes Care 2017;40:911–919

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A Telemedical Lifestyle Intervention Approach for Type 2 Diabetes

It might be possible to achieve significant reductions in HbA_{1c} in 12 weeks, along with generally improved metabolic health status, in advanced stage type 2 diabetes by following an intensive lifestyle management and intervention approach, according to Kempf et al. (**p. 863**). The conclusions are the result of a randomized controlled trial that compared the HbA_{1c} outcomes of patients with long-term type 2 diabetes following exposure to the Telemedical Lifestyle intervention Program (TeLiPro) or a controlled routine care scenario with minimal extra intervention. The primary result, according to the authors, was that the TeLiPro approach led to a drop of about 1.1% in HbA_{1c} readouts after 12 weeks, while the control subjects only managed about 0.2%. Treatment superiority of the approach reportedly remained up to 1 year later. Secondary outcomes, including weight reduction of 6 kg over the same period following the intervention, all point toward considerable improvements in health status for the patients according to the authors. While acknowledging some limitations in the trial—including a less than ideal dropout rate in the control group—the authors go on to speculate about how the approach might work in terms of the initial caloric restrictions of the approach and the subsequent feedback provided to improve outcomes. Author Kerstin Kempf said: "Type 2 diabetes is one of the few diseases in which the patients have the ability to actively influence their health status and progression of disease. By lifestyle change, the disease can not only be prevented, but even cured. TeLiPro strengthens patients' self-responsibility and enables them to implement lifestyle changes consistently and in the long-term. The goal should be improved glucometabolic control and quality of life with lower medication use. We would see TeLiPro as a qualitatively and economically valuable add-on to the national disease management programs in order to be able to guarantee comprehensive diabetes care in the future."

Kempf et al. Efficacy of the Telemedical Lifestyle intervention Program TeLiPro in advanced stages of type 2 diabetes: a randomized controlled trial. Diabetes Care 2017;40:863–871

Lifestyle Interventions or Metformin to Treat Type 2 Diabetes Are not Related to Cognitive Decline

Neither lifestyle interventions nor metformin used to treat type 2 diabetes has any effect on cognitive decline, according to Luchsinger et al. (**p. 958**) who report the outcomes of the latest analysis of the Diabetes Prevention Program Outcomes Study (DPPOS). This is despite the large body of evidence in literature that suggests type 2 diabetes may be a risk factor for cognitive decline and hence treating type 2 diabetes might also prevent it. The study followed up on a cohort of participants that took part in the Diabetes Prevention Program 12 to 14 years after original randomization with a battery of tests designed to assess cognitive performance. Approximately 750 participants in each group received either the intensive lifestyle interventions over the original study period, metformin, or placebo. In short, the authors report that there was no difference in cognition scores between any of the groups at either testing date, which they say does not support the hypothesis that treating type 2 diabetes reduces the risk of cognitive impairment. Reportedly the outcome is consistent with a similar finding from the Finnish Diabetes Prevention Study. As well as the main outcome, the authors also report an association between increased glycemia (HbA_{1c}) and poorer cognitive performance in the cohort and that metformin use appeared to be safe from a cognitive perspective. Concerns have been raised previously that the use of metformin may be associated with the risk of developing Alzheimer disease and, at least from the perspective of this cohort, that did not seem to be the case. Naturally, the finding of no apparent relationship could potentially be the result of confounding, bias, or lack of sensitivity of testing methods, and the authors discuss these aspects in detail. In short, they stand by the result but warn that longer-term follow-up still may reveal an association.

Luchsinger et al. Metformin, lifestyle intervention, and cognition in the Diabetes Prevention Program Outcomes Study. Diabetes Care 2017;40:958–965

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