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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Skipping Breakfast Alters Circadian Clock Gene Expression to Influence Glycemic Control in Type 2 Diabetes

Skipping breakfast likely leads to alterations in the way circadian clock genes are expressed with the result being altered glucose regulation, particularly after lunch. According to Jakubowicz et al. (**p. 1573**), this occurs in both healthy individuals and those with type 2 diabetes, but importantly it points to breakfast consumption as being a potential strategy for glycemic control in type 2 diabetes. Using a crossover study design, the authors randomly assigned healthy individuals (*n* = 18) and individuals with established type 2 diabetes (*n* = 18) to a test day with breakfast and lunch and a day with only lunch. Clock-related gene expression was then assessed in blood samples before and after the meals, along with plasma glucose, insulin, glucagon-like peptide 1 (GLP-1), and dipeptidyl peptidase IV activity. Skipping breakfast did alter gene expression, but in both healthy individuals and individuals with type 2 diabetes. Skipping breakfast also resulted in a notable drop in insulin response after lunch in individuals with type 2 diabetes while the glucose spike following lunch was much greater. In both groups, GLP-1 response was ~35% lower when breakfast was skipped. While the authors cover a number of genes involved in circadian rhythms, they highlight specifically that *Ampk* expression levels fell when breakfast was skipped but were upregulated when it was consumed. The significance? AMPK activation is known to stimulate glucose uptake, so the upregulation probably indicates improved glycemic control. According to author Oren Froy: "As breakfast skipping adversely affects clock and clock-controlled gene expression and is correlated with increased postprandial glycemic response, consumption of breakfast should be an important strategy when targeting glycemic control in type 2 diabetes. In addition, as the circadian clock controls all of our endocrine, metabolic, and physiological systems, regularity in meals could improve whole-body homeostasis and delay diabetes complications and other age-related diseases."

Jakubowicz et al. Influences of breakfast on clock gene expression and postprandial glycemia in healthy individuals and individuals with diabetes: a randomized clinical trial. Diabetes Care 2017;40:1573–1579

Nonadherence to Metformin Guidelines May Increase the Use of Second-line Antihyperglycemia Therapies

An analysis of claims data relating to antihyperglycemic medications suggests that a substantial proportion of type 2 diabetes patients are not initiated on or do not adhere to the recommended first-line therapy of two months' duration of metformin prior to initialization of second-line medications. Instead, it appears many are initiated on a second-line therapy (i.e., any other antihyperglycemia agent) much earlier or even without any metformin-based therapy. As a result, Tseng et al. (**p. 1500**), who conducted the analysis, suggest that apparent treatment failures of metformin might actually be attributable to nonadherence to guidelines. The study used insurance claims data from millions of individuals who were members of a health care benefits company in the U.S. After identifying ~52,000 individuals with type 2 diabetes, the researchers found that only ~8% of those that received second-line therapy also received prior metformin therapy for the recommended 60 days. A full 28% likely did not take metformin prior to receiving second-line therapy. To then account for the unknown levels of patients potentially using low-cost generic versions of metformin (i.e., prescriptions filled but not accounted for in the insurance-based data), the researchers detail a sensitivity analysis where they vary the rate of generics use from 0 to 45%. According to their estimates between 8 and 49% of individuals likely used metformin according to guidelines prior to starting second-line therapy. Author Kenneth D. Mandl provided some further analysis: "Even though pharmacy benefit managers have extensive real-time data about whether and when a patient has filled his or her prescriptions, this information rarely influences a physician's practice. Clinicians don't know if their patients are being adherent to the medications they prescribe. We have shown that at least some of the time, flying blind likely confuses physicians into thinking that poor adherence represents a lack of medication efficacy. And this leads doctors to move on to the next—and often more expensive—option."

Tseng et al. Antihyperglycemic medications: a claims-based estimate of first-line therapy use prior to initialization of second-line medications. Diabetes Care 2017;40:1500–1505

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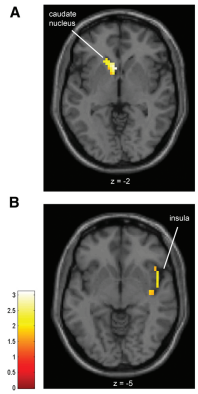
Roux-en-Y Gastric Bypass Surgery Affects Satiety: GLP-1 Implicated in Mechanisms

Roux-en-Y gastric bypass (RYGB) surgery can result in dramatic weight loss in obese individuals, and it is likely that most of the effect is the result of caloric restrictions. However, the effects of the operation might also diminish appetite, according to ten Kulve et al. (**p. 1522**). Specifically they report that the hormone glucagon-like peptide 1 (GLP-1) is likely to affect responses in the central nervous system to food cues leading to calorie intake reduction. The study involved 10 obese women who were scheduled to undergo RYGB surgery and a protocol that involved four functional MRI (fMRI) sessions where they were exposed to various visual food cues and actual food consumption. Two of the sessions took place before the operation, and two occurred after. Each set of sessions then randomly exposed the women to either a control infusion of saline or saline with the GLP-1 antagonist exendin 9-39 prior to the fMRI. The researchers report that post-operation, GLP-1 levels rose significantly after food intake as expected. There were also clear reductions in response in various areas of the brain to the food cues after the procedure compared with before the procedure (during placebo infusion). When they blocked GLP-1 receptors with exendin 9-39 and compared this with the placebo infusion, they found that the effect of GLP-1 on responses of the brain to the food cues were larger after the surgery compared with before the surgery. While explaining some of the mechanisms behind the weight-loss effects of the operation, the authors suggest it might represent a lead for the development of treatment strategies for obesity. Currently, one GLP-1 agonist is approved in the U.S. and Europe for use in treating obesity but the weight-loss effects are nothing like those typically achieved with bariatric surgery. Author Jennifer S. ten Kulve explained: "We believe that our findings provide further insights into the complex weight-lowering mechanisms of Roux-en-Y gastric bypass and the effect of the central regulation of feeding and the role of GLP-1 in this regulation."



Effects of GLP-1 blockade on central nervous system activation in response to visual (*A*) and gustatory (*B*) food cues.

ten Kulve et al. Elevated postoperative endogenous GLP-1 levels mediate effects of Roux-en-Y gastric bypass on neural responsivity to food cues. Diabetes Care 2017;40:1522–1529

Cognitive Decline in Type 2 Diabetes Related to Hyperglycemia

According to Geijselaers et al. (**p. 1537**), hyperglycemia and to some extent blood pressure most likely explain some of the cognitive deficits that are so often associated with type 2 diabetes. The authors now suggest that glycemic and blood pressure control should be considered to prevent diabetes-associated cognitive decline. They even suggest the same for individuals with prediabetes, which they readily admit will add to the debate on whether such individuals should be monitored and treated more intensively. The study used data from ~2,500 individuals who underwent an oral glucose tolerance test, a battery of cognitive performance tests, and a range of measures relating to insulin, HbA_{1c}, and blood pressure. They reportedly identified 666 individuals with type 2 diabetes, 386 with prediabetes, and the balance (~1,500) with normal glucose metabolism. The individuals with type 2 diabetes performed less well than individuals with normal glucose metabolism in all domains that the cognitive tests were designed to assess. The individuals with prediabetes though reportedly performed as well as the individuals with normal glucose metabolism. Hyperglycemia then explained most of the differences relating to the variables of processing speed and executive function and attention. Processing speed was also explained to some extent by blood pressure–related variables. The authors state that after adjusting for a variety of cardiovascular risk factors, the results did not change, likely indicating that glycemic load itself explains the cognitive deficits in type 2 diabetes. Commenting more widely on the study, author Coen D.A. Stehouwer told *Diabetes Care*: "Taken together, these results suggest that even comparatively mild hyperglycemia is crucially important in explaining differences in cognitive performance between individuals with and without type 2 diabetes. A key next step is to investigate whether these differences are reversible and preventable, notably by studying the effects on cognitive performance of meticulous glycemic control—as compared to usual care—in individuals with very early (for example, screen-detected) type 2 diabetes and prediabetes."

Geijselaers et al. The role of hyperglycemia, insulin resistance, and blood pressure in diabetes-associated differences in cognitive performance—the Maastricht Study. Diabetes Care 2017;40:1537–1547

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