

# In This Issue of *Diabetes*

Edited by Helaine E. Resnick, PhD, MPH

## Losartan May Slow the Progression of Some Features of Kidney Disease in American Indians With Type 2 Diabetes

In this issue of *Diabetes*, Weil et al. (p. 3224) report results from a randomized clinical trial of losartan treatment and show that among American Indians with type 2 diabetes, some features of diabetic nephropathy were slowed over 6 years of treatment. Although angiotensin II receptor blockers are commonly prescribed for type 2 diabetic patients with azotemia, whether they can prevent or slow the progression of early diabetic kidney disease is uncertain. In this new study, participants were stratified into two groups, normoalbuminuria ( $n = 92$ ) and microalbuminuria ( $n = 78$ ), and each group was randomized to either 100 mg losartan daily or placebo. Participants were followed for 6 years during which glomerular filtration rate (GFR) was measured annually and, at study end a kidney biopsy was performed to assess renal structure. The primary end point was decline in GFR to  $<60$  mL/min or half the baseline value among participants who entered the study with GFR  $<120$  mL/min. The study was underpowered to detect the primary end point because only nine individuals reached this outcome. However, the unadjusted hazard ratio was 0.50 in favor of losartan. A number of significant interactions between baseline renal function and treatment assignment were noted. In the microalbuminuria group, those taking losartan experienced a slower rate of expansion of mesangial fractional volume and maintained higher glomerular filtration surface density and area relative to placebo. By contrast, these effects were not observed in patients who began the study with normal albumin excretion. In the normoalbuminuria group, transition to macroalbuminuria was more frequent among those receiving losartan, but the opposite was true among those with baseline microalbuminuria. Data from this new study support the notion that diabetic individuals who have early signs of kidney disease may receive some renal protection from losartan. — *Wendy Chou, PhD*

Weil et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. *Diabetes* 2013;62:3224–3231

## Short-Term Impact of Intense Caloric Restriction on Glucose Regulation Similar to Gastric Bypass Surgery

This issue of *Diabetes* contains new data by Jackness et al. (p. 3027) suggesting that a very low-calorie diet (VLCD) induces the same short-term benefits on glucose regulation as Roux-en-Y gastric bypass surgery (RYGB). The newly published results shed light on an important question regarding which short-term feature of RYGB—the surgery itself or the caloric restriction that accompanies it—is responsible for rapid improvements that are often observed in glucose metabolism. In many cases, these benefits are seen before significant postsurgical weight loss occurs. This new study addressed this question by enrolling 11 patients scheduled for RYGB and 14 who were admitted to an inpatient clinic where they adhered to a controlled diet. The inpatient diet of 500 kcal/day was similar in nutrient content and total calories to the diet that was followed by the RYGB patients. The investigators collected data on numerous aspects of insulin sensitivity and  $\beta$ -cell function to determine how these diverse measures responded to the two interventions. A unique feature of the study is that the two groups were matched for both amount and rate of weight loss, a methodological feature that has been absent in previous attempts to explore RYGB-associated weight loss. The investigators showed that insulin sensitivity and  $\beta$ -cell function among participants on the VLCD were quite similar to their RYGB counterparts. However, Jackness et al. caution that longer-term studies are needed to understand the sustainability and clinical application of these results. — *Helaine E. Resnick, PhD, MPH*

Jackness et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and  $\beta$ -cell function in type 2 diabetic patients. *Diabetes* 2013;62:3027–3032

### Study Suggests Direct Effects of Atypical Antipsychotics on Glucose Regulation

A new study in this issue of *Diabetes* (p. 3232) indicates that atypical antipsychotic (AAP) medications have a direct impact on diverse aspects of glucose regulation, and that these effects occur independently of weight gain. In recent years, a significant increase in the prescribing of AAP medications has been accompanied by a persistent observation that some of these drugs increase the risk of obesity and type 2 diabetes. A basic question that has continued to elude investigators is whether the weight gain and increased diabetes that are often observed among patients using AAP medications are part of the natural history of the disease processes for which these medications are prescribed or if these unfavorable side effects result from the medications themselves. This question has potentially widespread implications because of the large number of individuals who use these agents as well as increasing off-label use in pediatric and elderly populations. Although previous studies have attempted to attribute obesity in AAP users to either the drugs or to schizophrenia/bipolar illness, these reports did not investigate mixed-meal challenges that mimic real-world conditions, and they did not control for physical activity, a potentially confounding factor in this relationship. The new data from Teff et al. address these methodological limitations by studying a sample of healthy individuals using an inpatient protocol in which activity and food intake were controlled. Thirty patients (ten in each group) were administered olanzapine, aripiprazole, or placebo for nine days. Glucose clamps and mixed-meal challenges were used to assess changes in glucose metabolism in these healthy subjects before and after AAP administration. Results showed that both olanzapine and aripiprazole induced insulin resistance, but olanzapine also resulted in unfavorable changes in postprandial hormones. The fact that these results occurred following short-term AAP administration in healthy patients and in the absence of changes in hunger or weight gain suggest that these agents act directly on tissues. — *Helaine E. Resnick, PhD, MPH*

Teff et al. Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease. *Diabetes* 2013;62:3232–3240

### Interrelationships Among Free Fatty Acids, Cardiovascular Risk Factors, and Insulin Resistance From Early Adolescence Into Adulthood

In this issue of *Diabetes*, Frohner et al. (p. 3163) present intriguing new findings on the evolution of relationships among circulating free fatty acids (FFAs), insulin resistance (IR), and cardiovascular disease (CVD) risk factors from late childhood to early adulthood. In obese individuals, an abundance of FFA can compete with glucose as an energy source, leading to glucose accumulation in serum and increased IR in muscle and liver. High FFA levels are also associated with several risk factors for CVD. In this new report, investigators extended an existing longitudinal analysis of 207 individuals to the mean-ages of 15 and 22 years. The study also added the subjects' parents ( $n = 272$  parents of 139 offspring) to understand how changes in children's risk factors related to those of their parents. The study assessed a number of factors including FFAs, fasting glucose, fasting insulin, insulin sensitivity, blood pressure, cholesterol, as well as a number of measures of adiposity. IR was determined by euglycemic-hyperinsulinemic clamp. At the mean-age of 15 years, FFAs were not correlated with IR, CVD risk factors, or adiposity. However, a significant inverse correlation between FFA levels and IR emerged at age 22 years, and this relationship strengthened into later adulthood. Over time, FFA levels became more closely linked to measures of CVD risk and adiposity. By middle age—represented by the parental group (mean-age 51 years)—FFAs were significantly associated with most CVD risk factors. These findings suggest that elevated FFAs lead to effects on metabolic disease that are not yet evident during adolescence, but which accumulate and manifest over the course of adulthood. The new report also provides novel evidence of FFAs as potential predictors of future IR. The authors suggest that early prevention of elevated FFAs may help delay or prevent the development of CVD in later adulthood. — *Wendy Chou, PhD*

Frohner et al. Relation between serum free fatty acids and adiposity, insulin resistance, and cardiovascular risk factors from adolescence to adulthood. *Diabetes* 2013;62:3163–3169

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