

Highlights From the Latest in Diabetes Research

Lifestyle Modification Slows Functional Decline in Type 2 Diabetes

Ample evidence supports the role of diabetes in increasing risk for both large- and small-vessel complications, as well as reducing quality of life and increasing health care costs. It has also been demonstrated that diabetes is associated with lower levels of physical function among middle-aged and older adults. The relationship between diabetes and disability can be viewed against the larger backdrop of the aging of the U.S. population and the role that disability plays in nursing home admission and loss of independence in the community. In an analysis of data from the Look AHEAD study, Rejeski et al. provide insight into what can be done to modify the trajectory of diabetes-associated mobility disability among community-dwelling adults. Look AHEAD participants included >5,000 diabetic individuals aged 45–74 years who were randomly assigned either to intensive lifestyle targeting a 7% weight loss and ≥ 175 min of weekly physical activity or to a control group that received diabetes education and support. Self-reported mobility was assessed with questionnaire items that were used to construct a 4-level outcome describing participants' mobility disability (good, mild, moderate, and severe). At 4 years, good mobility was present in 38.5 and 31.9% of intervention and control participants. Conversely, severe mobility disability was present in 20.6 and 26.2% of participants in the two groups. Tests of mediation were used to demonstrate that each 1% relative reduction in weight reduced the risk of mobility loss by 7.3% and that each 1% relative improvement in fitness reduced this risk by 1.4%. Although the Look AHEAD study was originally designed to examine the impact of intensive lifestyle modification on cardiovascular disease risk reduction among diabetic adults, Rejeski et al. have used this study vehicle to provide proof of concept that diabetes-associated disability can be favorably impacted by intensive lifestyle modification. However, the Diabetes Prevention Program (DPP) showed that a similar intervention was effective in reducing the risk of diabetes among high-risk individuals, yet widespread, sustainable translation of the DPP's resource-intensive methods has been elusive. The aging U.S. population will undoubtedly be impacted by diabetes-associated disability. A key challenge that lies ahead is identifying practical approaches to weight loss and fitness that will help older diabetic adults remain independent in the community.

— Helaine E. Resnick, PhD, MPH

- Rejeski et al. Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med* 2012;366:1209–1217

Bariatric Surgery More Favorable Than Medical Management in Advanced Type 2 Diabetes

Difficulties associated with achieving sustained weight loss are among the most challenging aspects of managing diabetic patients. These issues will be encountered by clinicians more frequently in the coming years as the numbers of diabetic individuals continue to increase in parallel with the obesity epidemic. Although efforts to promote weight loss are a staple of diabetes medical management, observational data from a number of studies suggested that bariatric surgery results in a greater degree of success in promoting both weight loss and glycemic control among diabetic patients. A pair of back-to-back studies extended findings from observational studies by randomly assigning obese diabetic patients either to medical management or to bariatric surgery and determining the impact of these divergent approaches on key outcomes.

The first study examined 150 patients who were randomly assigned to one of three groups: intensive medical therapy (IMT), IMT+Roux-en-X gastric bypass, or IMT+sleeve gastrectomy. Patients had mean HbA_{1c} of 9.2%, mean age of ~50 years, mean diabetes duration of >8 years, and mean BMI of 36 kg/m². Interestingly, 34% of patients had BMI <35 kg/m². The study's primary end point was the proportion of patients with HbA_{1c} $\leq 6\%$. At the conclusion of 12 months of follow-up, 12% of IMT patients had HbA_{1c} $\leq 6\%$ compared with 42% in the IMT+gastric bypass group and 37% in the IMT+sleeve gastrectomy group. In addition, mean HbA_{1c} was lower in both the IMT+gastric bypass and IMT+sleeve gastrectomy groups (6.4 and 6.6%) compared with that in the IMT group (7.5%). A number of other secondary outcomes including weight loss and use of lipid, glucose, and blood pressure-lowering drugs were also more favorable in the surgical intervention groups.

The second study randomly assigned 60 diabetic patients to one of three groups: IMT, gastric bypass, or biliopancreatic diversion. Entrance criteria included BMI >35 kg/m² and diabetes duration ≥ 5 years. The primary end point was the rate of diabetes remission defined by fasting glucose <100 mg/dL and HbA_{1c} <6.5% for ≥ 1 year. Mean BMI among these patients was ~45 kg/m², and mean diabetes duration was ~6 years. After 2 years of follow-up, no patients in the IMT group experienced diabetes remission, but remission occurred in 75% of the gastric bypass group and 95% of the biliopancreatic diversion group. Percent reductions in HbA_{1c}, fasting glucose, and body weight were higher in both surgical intervention groups compared with the IMT group. Total

cholesterol normalized in 27% of the IMT group and in 100% of both surgical intervention groups. Reductions or discontinuation of antihypertensive therapy was more similar across groups: 70, 80, and 85% in the IMT, gastric bypass, and biliopancreatic groups, respectively.

These studies provide compelling evidence of the potential utility of surgical interventions to address not only poor glycemic control but also a number of other unfavorable clinical features such as hyperlipidemia and hypertension that often accompany diabetes. It should be stressed that these studies were relatively small and short in duration, raising questions about whether these short-term benefits are sustained over longer periods of time. This work highlights the potential heterogeneity of response to surgical intervention and also raises much larger, highly controversial questions about the clinical context in which the rapidly increasing numbers of obese, difficult-to-manage patients should be approached in the future: medical or surgical? — H.E.R.

- Schauer et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012;366:1567-1576
- Mingrone et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. *N Engl J Med* 2012;366:1577-1585

Deletion of *Gpr21* Protects Against Obesity-Associated Inflammation and Insulin Resistance

Insulin resistance is not only a defining feature of type 2 diabetes but is also associated with chronic, low-grade inflammation. Part of the inflammatory response caused by obesity involves infiltration of macrophages into fat and liver. This infiltration can impair insulin action through cytokine secretion and through decreased suppression of hepatic glucose production. Elucidating the mechanisms underpinning obesity-induced macrophage transmigration may lead to novel targets for prevention or

treatment of type 2 diabetes. Recent data from Osborn et al. provide new insights into these mechanisms. In a series of experiments focusing on the GPCR family of receptors that sense extracellular signals, the investigators first demonstrated a high degree of expression of GPCR *Gpr21* in both the hypothalamus and adipose tissue of obese but not lean mice. Subsequently, they showed that *Gpr21* KO mice that were fed normal chow had lower body weight, improved glucose tolerance, and higher insulin sensitivity relative to their wild-type littermates. Experiments in mice that were fed a high-fat diet showed that KO and wild-type mice gained similar amounts of body weight, a fortuitous observation that permitted comparisons in weight-matched animals. Relative to their wild-type, weight-matched counterparts, KO mice had more favorable glucose tolerance, decreased insulinemia, and increased hepatic glucose suppression. Harvesting of adipose and liver tissue showed improved insulin action in KO mice, which had increased insulin-stimulated Akt phosphorylation in both tissues. Finally, both hepatic triglyceride and glycogen content were lower in KO mice. Additional experiments showed that observed improvements in insulin sensitivity could be traced to reduced inflammation associated with a decrease in chemotaxis of macrophages in KO mice. Taken together, these data suggest that GPR21 may be a promising target for additional work investigating whether obesity-induced insulin resistance can be addressed by controlling the proinflammatory response. — H.E.R.

- Osborn et al. G protein-coupled receptor 21 deletion improves insulin sensitivity in diet-induced obese mice. *J Clin Invest* 2012;122:2444-2453

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