In This Issue of *Diabetes*  
*Edited by Helaine E. Resnick, PhD, MPH*

### eNOS Drives Glucose Uptake in Adipose Tissue

Data in this issue of *Diabetes* show that endothelial nitric oxide synthase (eNOS)–derived nitric oxide (NO) is required in adipose tissue for mitochondrial biogenesis in response to exercise. These results add to a growing body of literature showing the importance of eNOS in mitochondrial biogenesis in a variety of tissues that are relevant in diabetes and glucose metabolism. A key feature of the new report by Trevellin et al. (p. 2800) is that the implications of earlier studies, which focused heavily on the role of eNOS in skeletal and cardiac muscle, have now been firmly extended to adipose tissue. In the new experiments, wild-type (WT) and eNOS−/− mice underwent a progressive exercise regimen, and data from these mice were compared with sedentary WT animals. In the WT mice that were exercised, mitochondrial biogenesis was higher than in the sedentary WT and eNOS−/− mice. Expression of peroxisome proliferator–activated receptor γ coactivator 1α (PGC-1α), which regulates mitochondrial biogenesis and function, was also higher in the trained WT animals compared with their eNOS−/− counterparts. Further, a link was demonstrated between exercise and both basal and insulin-stimulated glucose uptake in the WT mice but not the eNOS−/− mice. To understand the potential application of these observations in humans, the investigators studied subcutaneous adipose tissue samples from bariatric surgery patients. The experiments showed that NO promoted mitochondrial biogenesis in human adipocytes and also increased both glucose uptake and GLUT4 translocation. These results contribute to an evolution in thinking about the effect of NO in mediating the impact of exercise in adipose tissue, and they also raise important questions regarding the potential implications of these observations for the development of future therapies. — *Helaine E. Resnick, PhD, MPH*

### Bilirubin May Inhibit Progression of Nephropathy

A prospective analysis of bilirubin levels in two clinical trials of patients with diabetic nephropathy suggests that this antioxidant is associated with a reduced risk of nephropathy progression. In the new report by Riphagen et al. (p. 2845), investigators used data from two clinical trials—the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) studies—to extend earlier cross-sectional observations on the association between bilirubin and nephropathy. The earlier findings suggested that reduced bilirubin levels were associated with nephropathy in humans, but the temporal nature of this relationship remained unclear. In the newly published longitudinal analyses, baseline bilirubin levels were measured for more than 3,000 people with diabetic nephropathy who were enrolled in the two trials, and these levels were related to a composite end point consisting of either a doubling of serum creatinine or end-stage renal disease. Notably, patients were followed for an average of 3.4 years in RENAAL and 2.6 years in IDNT, and the analyses accounted for changes over time in both bilirubin and a variety of other clinical factors that were measured repeatedly during follow up. In the RENAAL study, 31% of patients progressed to the renal end point, and 22% progressed in IDNT. In both studies, total bilirubin was associated with a significant reduction in the risk of progressing to the renal end point. In RENAAL, the hazard ratio was 0.54, and it was 0.64 in IDNT. These observations were robust despite adjustments for potential confounders as well as a series of sensitivity analyses, and they support the earlier cross-sectional observations suggesting that bilirubin may have a protective effect against the progression of renal damage in diabetes. The findings also suggest that measurement of this antioxidant may be helpful in predicting the risk of progression of kidney disease among people with diabetes. — *Helaine E. Resnick, PhD, MPH*

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**Trevellin et al.** Exercise training induces mitochondrial biogenesis and glucose uptake in subcutaneous adipose tissue through eNOS-dependent mechanisms. *Diabetes* 2014;63:2800–2811

**Riphagen et al.** Bilirubin and progression of nephropathy in type 2 diabetes: a post hoc analysis of RENAAL with independent replication in IDNT. *Diabetes* 2014;63:2845–2853
Combi-GAD Therapy Reverses Diabetes in Recent-Onset NOD Mice

Autoantigen-specific therapies are an appealing strategy to combat the loss of tolerance in patients with type 1 diabetes because they target only β-cell–reactive T cells, thereby resulting in fewer side effects than other therapeutic approaches. However, while numerous preclinical models have shown promise in restoring tolerance, they have faltered in clinical trials. Results from a new report in this issue of Diabetes by Robert et al. (p. 2876) may move this challenging field forward using a novel, antigen-specific combination therapy involving glutamic acid decarboxylase (GAD)-65. Although orally administered GAD65 has not demonstrated efficacy in the past, the authors of this new study hypothesize that the failure of earlier work involving oral GAD65 administration may have been caused by degradation of the compound in the stomach, leading to insufficient delivery to the gut. In this work, Robert et al. tested whether oral administration of genetically modified Lactococcus lactis (L. lactis) expressing GAD65, IL10, and an anti-inflammatory cytokine, combined with short-course, low-dose anti-CD3, could reverse diabetes in recent-onset NOD mice. L. lactis was chosen as a method of secreting antigen to the intestine based on earlier success with this delivery system. NOD mice received oral administration of L. lactis-secreting GAD65, or with or without an initial course of systemic low-dose anti-CD3. L. lactis treatment combined with anti-CD3 (combi-GAD) resulted in more mice returning to normoglycemia than L. lactis or anti-CD3 alone. Remission using combi-GAD therapy lasted at least 8 weeks following the end of treatment, and treated mice maintained stable glycemia once they normalized. Notably, combi-GAD was equally effective in mice with both mild and severe hyperglycemia (>350 mg/mL) at diagnosis. Taken together, these results suggest that orally administered combi-GAD therapy may be a promising strategy for inducing tolerance in type 1 diabetes. Despite these encouraging results, well-recognized difficulties associated with moving preclinical promise into clinical success with antigen-specific approaches dictate the need for additional work to determine whether data from animal models have application in humans. — Laura Gehl, PhD

Key Role for Heparanase in Lipoprotein Lipase Transfer in Diabetes

A new study suggests that the inhibition of heparanase could offer a novel approach to managing cardiomyopathy in diabetes. In patients with diabetes, the heart has a greater need for fatty acid (FA) than in people without diabetes. A large amount of this FA comes from coronary lipoprotein lipase (LPL) breaking down plasma triglycerides. In a new report published in this issue of Diabetes, Wang et al. (p. 2643) investigated the mechanism by which LPL is sent to the coronary lumen in response to hyperglycemia. In order for the enzyme to move from cardiomyocytes to the lumen, LPL must be released from the myocyte surface proteins heparan sulfate proteoglycans (HSPGs). In the new study, endothelial cells (EC) were cocultured with myocytes and, after exposure to high glucose levels, the investigators assessed uptake of endothelial heparanase into the myocytes. These experiments showed that the myocytes took up heparanase from EC via a caveolae-dependent pathway using HSPGs. The heparanase was then converted from a latent to an active form in the myocyte lysosomes. After entering the nucleus, heparanase increased the expression of matrix metalloproteinase (MMP)-9, an enzyme that is associated with vascular permeability. A key observation of the new report was that HSPGs were shed from the surface of the myocytes, thereby freeing LPL to move to the coronary lumen. To understand these findings in a diabetes model, male rats with streptozotocin-induced diabetes were found to have an accumulation of heparanase in the myocyte nucleus. An increase in MMP-9 expression was also observed in the same animals, and HSPGs were shed at an accelerated rate following hyperglycemia. These results suggest that EC-derived heparanase allows cardiomyocytes to send LPL to the coronary lumen. In patients with diabetes, the FA resulting from this response to hyperglycemia can eventually cause lipotoxicity in the heart, ultimately resulting in cardiomyopathy. Inhibition of heparanase may therefore warrant exploration as a novel strategy to manage diabetic cardiomyopathy. — Laura Gehl, PhD

DOI: 10.2337/db14-ti08

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