Why Might Thiazolidinediones Increase Exercise Capacity in Patients With Type 2 Diabetes?

Individuals with type 2 diabetes are insulin resistant and as a group have a lower exercise capacity ($V\text{O}_{2max}$) than age- and weight-matched people without diabetes (1,2). In this issue, Regensteiner et al. (3) report that rosiglitazone (RSG), a thiazolidinedione (TZD) commonly used to treat insulin resistance, also improves exercise capacity in patients with type 2 diabetes. Following 4 months of treatment with 4 mg/day RSG, the authors observed expected improvements in insulin sensitivity as determined by homeostasis model assessment and a hyperinsulinemic-euglycemic clamp in 10 middle-aged men and women with type 2 diabetes. A novel finding was that RSG caused a modest but significant increase in $V\text{O}_{2max}$ (1.4 $ml \cdot kg^{-1} \cdot min^{-1}$ or ~7.1%). These observations raise three fundamental questions: *1*) Why is type 2 diabetes associated with a decrease in exercise capacity? *2*) How might TZDs, such as RSG, counteract this? and *3*) Is the effect of RSG on exercise capacity likely to be clinically relevant?

Recent studies suggest several explanations for the decrease in $V\text{O}_{2max}$ in patients with type 2 diabetes. One of these is the presence of mitochondrial dysfunction. As reported by Kelley et al. and Ritov et al., (4–6) skeletal muscle of sedentary middle-aged individuals with established type 2 diabetes (HbA_{1c} 8.0 ± 0.2%) exhibits reduced mitochondrial oxidative enzyme (succinate dehydrogenase) activity and electron transport chain capacity (rotenone-sensitive NADH:O_2 oxidoreductase activity) (~26 and 59%, respectively), smaller mitochondria, and higher intramyocellular triglyceride content than muscle of normal control subjects. Their data also suggested that subsarcolemmal mitochondria were especially affected. In addition to these findings, Mootha et al. (7), using a strategy referred to as Gene Set Enrichment Analysis, profiled >22,000 genes in a muscle biopsy and identified a subset of ~100 coregulated oxidative phosphorylation genes in which expression was significantly reduced (~20%) in men (65.5 ± 1.8 years) with type 2 diabetes. They noted that the expression of the vast majority of these genes is under the control of peroxisome proliferator–activated receptor γ (PPARγ) coactivator 1α (PGC-1α), a transcriptional regulator of mitochondrial biogenesis whose abundance is also reduced (~20%) in type 2 diabetes. In addition, they observed a close relationship between the expression of this subset of mitochondrial genes and $V\text{O}_{2max}$. Similar alterations in PGC-1α and PGC-1α–responsive genes were reported in younger (~45 years) men and women with type 2 diabetes by Patti et al. (8). Whether alterations in mitochondrial genes are a primary event (hereditary) in these patients or are secondary to genetic or acquired abnormalities in cellular fuel metabolism due to nutrient excess or inactivity remains to be determined.

A second factor that could lead to a decrease in $V\text{O}_{2max}$ in patients with type 2 diabetes is impaired muscle blood flow. Endothelial dysfunction, as manifest by impaired flow-mediated vasodilation (increase in brachial artery diameter following postocclusion-induced hyperemia), diminished acetylcholine-induced vasodilation (9), or an impaired ability of insulin to increase muscle blood flow (10), has been described in patients with type 2 diabetes. The increase in O_2 use by muscle during incremental exercise is in part mediated by its ability to extract oxygen from the blood, an adaptation that appears to involve vasodilation of terminal arterioles and a resultant increase in capillary surface area in the working muscles. Clark et al. (11) have noted that it is by such a mechanism that exercise and insulin stimulate a shift from nonnutritive to nutritive blood flow in skeletal muscle and that this effect is enhanced by exercise training and impaired by insulin resistance and factors that cause it (e.g., inflammatory cytokines). The relative physiologic importance of this disturbance in blood flow versus mitochondrial abnormalities and other factors (e.g., myocardial dysfunction, genetic differences in muscle fiber type) to the decreased $V\text{O}_{2max}$ in patients with type 2 diabetes remains to be determined. As will be discussed later, a closely related abnormality that could play a role in diminishing $V\text{O}_{2max}$ is dysregulation of the fuel-sensing enzyme AMP-activated protein kinase (AMPK).

TZDs, such as RSG, could improve $V\text{O}_{2max}$ by multiple mechanisms. First, by binding to the PPARγ in adipose tissue, presumably the major target of TZD action (12), they enhance the transcription of genes that stimulate preadipocyte differentiation and increase fatty acid transport, synthesis, and storage in adipose tissue. These actions in turn lead to decreased levels of plasma free fatty acids and intramyocellular and intrahepatic triglycerides, events widely believed to contribute to the ability of TZDs to diminish cellular lipotoxicity and secondarily attenuate insulin resistance and mitochondrial and endothelial cell dysfunction (13).

TZDs could also enhance $V\text{O}_{2max}$ by modifying the synthesis and release of a number of adipocyte-derived signaling molecules (adipokines) that affect both insulin sensitivity and vascular function (e.g., brachial artery diameter). One of these molecules is adiponectin, a robust insulin sensitizer whose concentration is decreased in people with obesity, type 2 diabetes, and coronary heart disease as well as in individuals at increased risk for these disorders (14,15). Treatment with TZDs causes an approximately twofold increase in plasma adiponectin in patients with type 2 diabetes (16). Adiponectin, like insulin, has been reported to stimulate the production of nitric oxide in vascular endothelial cells (17) and to diminish endothelial dysfunction caused by tumor necrosis factor α and other factors in cultured cells (18). In addition, it has been demonstrated to diminish ectopic lipid deposition, a close correlate of insulin resistance and cellular dysfunction, in muscle and liver (19,20).

Intriguingly, adiponectin links RSG and other TZDs to AMPK (21,22). Thus, adiponectin has been shown to increase

AMPK activity in rodent tissues in vivo and in vitro (22,23), and the ability of chronic TZD therapy to activate AMPK is diminished in adiponectin knockout mice (A. Nawrocki, E. Tomas, N.B.R., P. Scherer, unpublished data). On the other hand, acute (within 30 min) effects of TZDs on AMPK activity have been observed in rodent tissues in vivo (N.K.L., M. Kelley, E. Tomas, N.B.R., unpublished data) and in cultured cells (24), suggesting that TZDs may also activate AMPK by other mechanisms. Exercise and another insulin-sensitizing drug, metformin, have also been shown to activate AMPK in various rodent tissues; however, the mechanism by which they do so is incompletely understood. Interestingly, activation of AMPK in muscle and other tissues leads to increases in fat oxidation, induction of PGC-1α and genes governing mitochondrial biogenesis and enzymes of oxidative phosphorylation, and protection against the lipotoxic effects of excess fatty acids and cytokines (e.g., in liver, muscle, endothelium, and pancreatic β-cells) (rev. in 15). Conversely, decreases in its activity have been observed in a number of rodents with insulin resistance, as well as in the interleukin-6 knockout mouse in which it is associated with a decreased capacity for exercise (25). In addition, TZDs and the AMPK activator, AICAR, have also been shown to prevent the development of diabetes in the Zucker diabetic fatty rat, a rodent with a defective leptin receptor and diminished AMPK activity that typically becomes obese and severely hyperglycemic as it ages (26). Whether they prevent mitochondrial and endothelial cell dysfunction in these animals is unknown.

In summary, the study by Regensteiner et al. suggests that in addition to improving insulin sensitivity, TZDs may increase exercise capacity in patients with established type 2 diabetes. Its effects on $V_{O_{2max}}$ in the present study were modest, suggesting that their efficacy for this purpose in people with established type 2 diabetes may be limited or that a period of treatment in excess of 4 months is needed. Such findings also raise the question of whether treatment with TZDs or possibly other AMPK activators would be more effective if started earlier. In this regard, evidence of mitochondrial dysfunction, insulin resistance, and decreased $V_{O_{2max}}$ has been observed both in people with impaired glucose tolerance (7) and in euglycemic offspring of patients with type 2 diabetes (8). To what extent these individuals would benefit clinically from treatment with TZDs, diet and exercise, or metformin remains to be determined.

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