Insulin Resistance and a Long, Strange Trip

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"What a long, strange trip it's been" is how the late Jerry Garcia and the Grateful Dead reflected on the ups and downs of life in a famous song. Clinicians might use the same phrase to describe the search for ways to treat insulin resistance, which is very common.

Insulin binds to its receptor to activate intracellular signaling that regulates nutrient metabolism, growth, fluid homeostasis, blood-vessel tone, and other functions. When confronted with excess adiposity, cells dampen insulin-receptor signaling to resist the effects of insulin. This impaired signaling elevates lipids through a lack of suppression of fatty acid release by adipose tissue, increases glucose owing to impaired stimulation of glucose transport, and raises blood pressure as a consequence of deficient nitric oxide release. Combinations of clinical features of insulin resistance — hypertriglyceridemia, a low level of high-density lipoprotein cholesterol, a fasting glucose level of more than 100 mg per deciliter (5.6 mmol per liter), hypertension, and central adiposity — constitute the metabolic syndrome, which affects 23% of American adults.[1] Insulin resistance is present in most of the 69% of American adults who are overweight or obese.[1]

By the 1980s, insulin resistance was accepted as a contributor to atherosclerotic complications such as stroke and heart attack,[2] which prompted a search for insulin sensitizers to decrease vascular disease. Peroxisome proliferator–associated receptors (PPARs), nuclear receptors that orchestrate responses to nutrients, were identified in the 1990s, and insulin-sensitizing thiazolidinediones were recognized to activate PPAR-γ. These drugs, which were approved to treat diabetes, gained wide acceptance. One drug in this class, troglitazone, which was included in the Diabetes Prevention Program,[3] was removed from the market because of liver toxicity. Rosiglitazone and pioglitazone were associated with congestive heart failure. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial,[4] investigators found that the use of pioglitazone in patients with type 2 diabetes and vascular disease reduced a composite secondary end point of death, nonfatal myocardial infarction, and stroke but increased the rates of edema, weight gain, heart failure, and bladder cancer. Rosiglitazone was implicated in heart attacks, and its use was restricted. In addition, bone fractures were associated with this class of drugs. Thiazolidinediones fell from grace. Even though a 6-year review of rosiglitazone did not confirm a risk of heart attack[5] and a 10-year review of pioglitazone did not confirm an increased risk of bladder cancer,[6] these agents were mostly relegated to use in unusual conditions such as lipodystrophies.

Amid this turmoil, a dedicated group of investigators kept on truckin' to conduct the Insulin Resistance Intervention after Stroke (IRIS) trial,[7] with results now reported in the *Journal*. IRIS investigators pursued the hypothesis that pioglitazone would decrease vascular events in patients without diabetes who had insulin resistance and a history of stroke or transient ischemic attack. Trial patients were found to have insulin resistance on the basis of their score on the homeostasis model assessment of insulin resistance (HOMA-IR) index. Elevated fasting insulin levels reflect insulin resistance, and relating insulin to fasting glucose (accomplished by the HOMA-IR score) provides a reliable metric. At baseline, more than 90% of the trial patients were taking antiplatelet or antithrombotic medications, more than 80% were nonsmokers, more than 75% took statins, and more than 60% had a blood pressure under 140/90 mm Hg.

The results of the trial are surprising. Despite having a history of very effective cerebrovascular treatment, patients who were assigned to the pioglitazone group were 24% less likely than those in the placebo group to have a stroke or heart attack (the primary outcome) at 5 years. How pioglitazone decreased vascular events is not clear. Several risk factors decreased among the trial patients (including systolic blood pressure and levels of fasting glucose and triglycerides), but low-density lipoprotein cholesterol levels increased. Patients in the pioglitazone

group had a reduced rate of progression to diabetes, which confirmed the findings of other studies of thiazolidinediones. There was no effect on heart failure or cancer, but patients in the pioglitazone group were more likely to stop the study drug than were those in the placebo group. Pioglitazone was associated with weight gain, edema, and serious fractures, which are all known side effects of thiazolidinediones.

These findings may tempt clinicians to rush to prescribe pioglitazone, but many caveats remain. Patients in the IRIS trial met strict criteria (including exclusion for heart failure) and were enrolled on the basis of standardized insulin assays. Patients had little neurologic impairment, and the response to pioglitazone may be different among those with substantial deficits. However, pioglitazone represents a potentially important therapy for the secondary prevention of vascular events in appropriately selected patients with cerebrovascular disease. The results of the IRIS trial should stimulate the search for precision-medicine approaches to vascular disease. Variants in PPAR-γ binding sites modulate drug responses,[8] which suggests that genetic profiling of patients with insulin resistance could identify those who are likely to benefit from pioglitazone while avoiding adverse effects. Profiling should include PPAR-α target genes since pioglitazone is also a ligand for PPAR-α, the activation of which decreases retinal vascular disease in patients with insulin resistance.[9,10]

It has taken two decades to show that an insulin sensitizer decreases vascular events in patients selected for insulin resistance. Insulin-sensitizing drugs have been exalted as metabolic saviors and vilified as a threat to public health. The trip has been long and strange, but it may yet lead to strategies for improving the health of people like Jerry Garcia, whose premature death was related to insulin resistance.

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