PERSPECTIVE

Causation of Type 2 Diabetes — The Gordian Knot Unravels

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Type 2 diabetes has always been a snake in the grass, sneaking up on both those with the disease and their physicians. To whit, the term "mild diabetes" persists, even though the disease is a leading cause of premature death from cardiovascular causes, amputations, and blindness. Life expectancy is considerably worse after the diagnosis of type 2 diabetes than after the diagnosis of some types of cancer. Moreover, the incidence of this condition is currently increasing so rapidly that it has been referred to as a pandemic. Basic concepts of the causation of type 2 diabetes have changed little for more than two decades, and progress in this field has appeared to be as difficult as untying the Gordian knot of mythology. However, the article by Petersen and colleagues in this issue of the *Journal* (pages 664–671) brings a welcome new direction to the field.

Let us consider the insights of the past decade that formed the springboard for this apparent breakthrough. First, insulin resistance in muscle is the earliest detectable defect in persons in whom type 2 diabetes will later develop. Second, beta-cell function has to be abnormal before hyperglycemia develops. This decline in function begins an estimated 10 years before diabetes is diagnosed, at which time beta-cell function is typically about 30 percent of the normal level. The United Kingdom Prospective Diabetes Study confirmed that this inexorable decline in beta-cell function was the same irrespective of treatment with dietary interventions alone, sulfonylurea, metformin, or insulin.

A third observation of note allowed us to escape from the glucose-only view of diabetes. A remarkable excess accumulation of intracellular triglyceride in both muscle and liver has been demonstrated to occur in type 2 diabetes. Knowledge about substrate competition between lipid and glucose suggested that this lipid accumulation contributed to insulin resistance. Further studies strongly suggested that the increased intracellular lipid stores in muscle predate the clinical onset of type 2 diabetes by many years.

In the mid-1990s, troglitazone was shown to improve insulin sensitivity in humans by interacting with a nuclear receptor, the peroxisome-proliferator–activated receptor γ (PPARγ). This drug improved glucose control in patients with type 2 diabetes, but the subsequent demonstration that troglitazone actually delayed the decline in beta-cell function and prevented the onset of type 2 diabetes in a high-risk population was exciting.[1] No other drug had previously affected the natural history of the development of type 2 diabetes. Ensuing work has shown that the newer agents pioglitazone and rosiglitazone also appear to have the remarkable ability to protect the beta cell as well as improve insulin sensitivity. However, these drugs do not prevent the terminal decline in beta-cell function after the onset of symptomatic diabetes.

As a consequence, the biology of PPARγ has been vigorously probed. A coactivator of the receptor, peroxisome-proliferator–activated receptor γ coactivator 1 (PGC-1), has been discovered, and a common polymorphism of PGC-1 has been identified in patients with type 2 diabetes in population-based studies.[2] Overweight people with a family history of type 2 diabetes have decreased expression of *PGC-1*, even when glucose tolerance is still normal.[3]

Since PGC-1 is a transcriptional coactivator that is essential for the synthesis of the mitochondrial enzymes for the beta-oxidation of fatty acid, the relevance of an apparently unrelated line of research becomes clear. Studies of triglyceride accumulation in muscle led to the recognition of a diabetes-associated decrease in the activity of the enzymes that are responsible for lipid oxidation, a process located almost exclusively in mitochondria. Recent biopsy studies in patients with type 2 diabetes have shown that mitochondria have impaired oxidative capacity and are only 55 percent of their normal size.[4]

Petersen and colleagues report changes in mitochondrial function that potentially link the twin defects in muscle and beta-cell function in type 2 diabetes. They used the elegant technique of saturation-transfer magnetic resonance spectroscopy to measure the rates of ATP synthesis in vivo (see Figure). The rate of mitochondrial ATP synthesis in skeletal muscle was decreased by 30 percent in a group of young, lean, insulin-resistant offspring of parents with type 2 diabetes, as compared with a

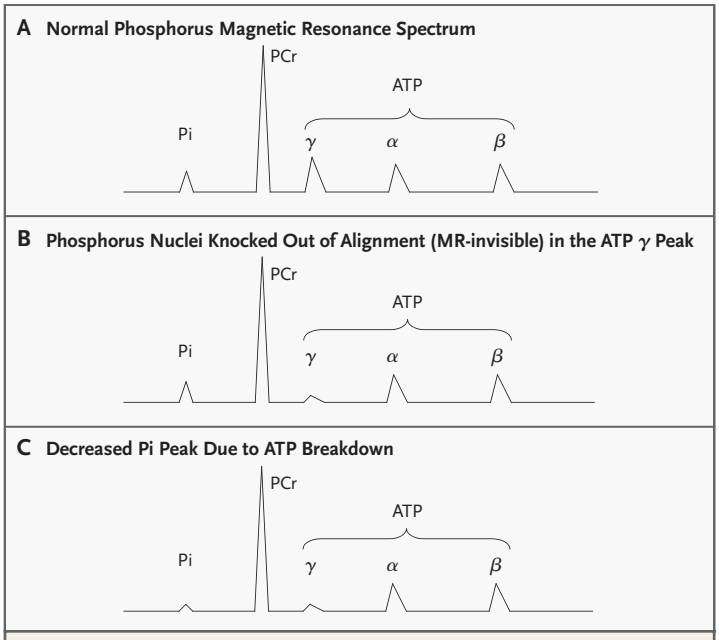

Figure. The Use of Saturation-Transfer Magnetic Resonance Spectroscopy to Measure the Rates of ATP Synthesis in Muscle.

In this schematic of a phosphorus-31 magnetic resonance spectrum from human muscle, the area under each peak is proportional to the concentration of the particular compound. The generation of a spectrum such as that shown in Panel A depends on the parallel alignment of the magnetic axes of the atomic nuclei with the magnetic field. If the nuclei in one compound are knocked out of alignment by a radiofrequency pulse tuned to the characteristic frequency for, say, ATPγ, then the spectrum measured immediately afterward will look like that shown in Panel B. The phosphorus atoms of ATP have, in effect, been labeled by becoming invisible on magnetic resonance imaging, and a short-lived, endogenously derived tracer has been created. The subsequent movement of these "labeled" phosphorus atoms into other compounds can be tracked. Since there is a continuous interchange of phosphorus between ATP and inorganic phosphorus (Pi), with ATP synthesis and breakdown, the signal from the inorganic phosphorus peak will decrease within milliseconds (Panel C). The quantitation of the areas under the peaks permits the calculation of the rate of mitochondrial ATP synthesis. PCr denotes phosphocreatine.

group of control subjects with normal insulin sensitivity who were matched for physical activity. The findings suggest that an inherited defect in mitochondrial oxidative phosphorylation could lead to lipid accumulation and hence underlie the insulin resistance in muscle. A similar inherited tendency might be postulated to explain the progressive decrease in beta-cell function.

Might this study represent a definitive breakthrough in our understanding of type 2 diabetes? The implication of recent observations, taken together, is that a moderate deficiency in the action of PGC-1 or related factors may underlie the mitochondrial dysfunction, as reflected in somewhat subnormal rates of lipid oxidation. This dysfunction could explain a steady tendency toward both weight gain and excess intraorgan lipid levels.

It is notable that the typical bioenergetic properties of mitochondria in type 2 diabetes are also present in obesity.[4] We know that the population rates of diabetes are dependent on physical inactivity and adiposity, phenomena that can now be explained. Weight loss would be expected to offset the metabolic effects of the subtle mitochondrial defect. Similarly, physical exercise increases mitochondrial gene expression and oxidative capacity, possibly through increases in PGC-1 levels. Aging is associated with declining mitochondrial function and decreased rates of muscle ATP synthesis.[5] Thus, separate influences of genetic and environmental factors increase the prevalence of type 2 diabetes with increasing age.

The same processes appear likely to affect the beta cell, as well as muscle. Mitochondria play a critical role in mediating glucose-induced insulin secretion, and islets that are exposed to increased lipid levels in vitro exhibit inhibition of insulin-gene expression. Indeed, a sudden and massive increase in islet triglyceride levels occurs just before the onset of hyperglycemia in some animal models of diabetes. The administration of troglitazone both decreases islet lipid levels and prevents the onset of diabetes.

A number of new hypotheses now unfold. Do obese, inactive people who retain normal glucose tolerance lack the susceptibility-related polymorphism of PGC-1? Do moderately overweight people in whom type 2 diabetes develops in early adult life have multiple genetic "hits" affecting pathways involving PGC-1? What is the dose–response relationship between the exercise-induced stimulation of mitochondrial activity and the prevention of diabetes? At what stage of incipient beta-cell failure will glitazones and other therapies that influence PPARγ be most effective? Will this effect be magnified by concurrent therapy with fibrate drugs — now known to be agonists of peroxisome-proliferator–activated receptor α (PPARα)?

Management of type 2 diabetes has always been centered on control of the body's energy economy — the attempt to achieve a negative calorie balance and the achievement of the optimal intake of carbohydrates and lipids. These latest studies permit us to peer into the powerhouse of the cell in order to bring causation and pathogenesis into sharper focus.

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Preeclampsia — Searching for the Cause

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Three to 5 percent of pregnancies in the United States are complicated by preeclampsia, a multisystem disorder characterized by hypertension and proteinuria that occurs after 20 weeks of pregnancy. Preeclampsia is associated with substantial risks. For the fetus, these include intrauterine growth restriction, death, and prematurity with attendant complications, whereas the mother is at risk for seizures (eclampsia), renal failure, pulmonary edema, stroke, and death. Despite considerable research, the cause or causes of preeclampsia remain unclear, and there are no clinically useful screening tests to identify women in whom it will develop. Antihypertensive therapy lowers maternal blood pressure but does not improve fetal outcomes; the only "cure" is the delivery of the infant.

Preeclampsia has been dubbed the "disease of theories" because of the multiple hypotheses proposed to explain its occurrence. It is recognized that abnormal placentation and placental vascular insufficiency (see Figure) are core features of preeclampsia, but why these and associated systemic abnormalities occur remains uncertain. Among the many proposed causes are immunologic derangements (a maternal immune reaction to paternal antigen in the placenta), genetic factors, increased insulin resistance (and associated elevations in the levels of insulin, free fatty acids, and triglycerides), dietary calcium deficiency, increased oxidative stress, and prostaglandin imbalance (an increased ratio of thromboxane levels to prostacyclin levels). Preeclampsia is likely to be multifactorial in origin, and characteristics of the mother and the placenta may interact to lead to its development.

Recent research has focused on endothelial dysfunction as a central abnormality in preeclampsia. Abnormal pressor responsiveness in this disorder was recognized decades ago, when it was observed that women in whom preeclampsia was later diagnosed first lost the refractoriness to infused angiotensin II that is characteristic of normal pregnancy. More recent studies in preeclamptic women have demonstrated increased levels of factors associated with abnormal endothelial function, such as cytokines (e.g., tumor necrosis factor α) and endothelin-1.

Clinical research into factors that may cause preeclampsia has been complicated by the misclassification of study subjects, since not all hypertension in pregnancy is due to preeclampsia. Gestational hypertension — elevated blood pressure without proteinuria or other systemic manifestations — is frequently confused with preeclampsia but usually has a benign course. Other women who are labeled as having preeclampsia have unrecognized chronic hypertension. It is also unclear whether many abnormalities observed in women with preeclampsia are primary (causal) or are secondary to the disease process. At the same time, the lack of an animal model of preeclampsia has hampered laboratory research into this condition.

Given the uncertainty regarding the cause of preeclampsia, it is not surprising that effective interventions are lacking to prevent its occurrence. Despite encouraging preliminary observations, large studies of interventions based on hypothesized causes of preeclampsia have yielded inconsistent and often disappointing results. In randomized trials sponsored by the National Institutes of Health that were previously reported in the *Journal*, low-dose aspirin[1]