Metabolic Rehabilitation
Science Gathers to Support a New Intervention to Prevent Stroke

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Type 2 diabetes is a well-recognized risk factor for cerebrovascular disease. In this issue of Stroke, Thacker et al\(^1\) demonstrate that earlier abnormalities in carbohydrate metabolism, insulin resistance, and impaired glucose tolerance are also associated with increased risk for cerebral ischemic events. These findings are reliable and timely, and they have immediate implications for the design of the next generation of stroke prevention trials.

Abnormal carbohydrate metabolism comprises a spectrum of disorders characterized by impaired energy utilization. Early manifestations include obesity, decreased insulin sensitivity, impaired fasting glucose, and impaired glucose tolerance. The latter 2 conditions are often referred to as “prediabetes,” a stark description of their typically progressive nature. The most advanced manifestation, type 2 diabetes, results from the inexorable loss of insulin secretory capacity in the face of well-established insulin resistance. These metabolic states have become endemic in most countries as westernized lifestyles are adopted. In the United States alone, there are now 26 million individuals with diabetes and 79 million with prediabetes. Globally, the number of diabetic patients is now estimated to be 366 million.

Clinicians who care for stroke patients know that metabolic disease is also prevalent in this population. Among patients with ischemic cerebrovascular disease, 18% to 30% are obese, 25% to 30% are insulin-resistant, 23% to 28% have impaired glucose tolerance, and 13% to 36% have diabetes.\(^2\)\(^-\)\(^5\)

The Figure illustrates a model of impaired glucose regulation and its potential causal relationship to stroke. Each of its cardinal manifestations (ie, obesity, insulin resistance, hyperglycemia, diabetes) have been associated with increased risk for stroke.\(^6\) However, the evidence is strongest for obesity and diabetes, possibly because these are easiest to measure and classify. Obesity (body mass index $\geq 30$ kg/m$^2$) doubles the risk for ischemic stroke, although the effect appears to be substantially mediated by coexistent cardiovascular risk factors.\(^7\)\(^-\)\(^8\) Importantly, not all obese patients exhibit these complications; ~25% of those with obesity lack additional evidence for the metabolic syndrome. That is, they do not have hypertension, dyslipidemia, hyperglycemia, or evidence of vascular inflammation, insulin resistance, or endothelial dysfunction that typically characterize this condition.\(^9\) Adipose tissue topography may explain some of these differences because patients with so-called uncomplicated obesity may have fat distributed preferentially to more metabolically quiescent sites, such as arms, legs, and buttocks,\(^9\) as opposed to the more metabolically active centripetal sites, including liver and omentum. It is not surprising, therefore, that waist-to-hip ratio (a reflection of central obesity) has a closer association with stroke risk than body mass index (odds ratio adjusted for risk factors including diabetes and body mass index $=3.0$; 95% confidence interval, 2.1–4.2).\(^10\)

Obesity is a major contributing risk factor to the development of insulin resistance, leading to type 2 diabetes. Patients with diabetes have 2- to 3-times the risk of ischemic stroke compared with nondiabetic patients after adjusting for blood pressure and other risk factors.\(^6\)\(^-\)\(^11\) In addition, on average patients with diabetes tend to have strokes ~2 years earlier than nondiabetic patients.\(^12\)

The distinct importance of the study by Thacker et al is in confirming that prediabetic conditions, including insulin resistance and postload hyperglycemia, are associated with increased risk for stroke. The investigators conducted an observational cohort study of 3442 community-based participants in the Cardiovascular Health Study who were free of stroke and diabetes at baseline. To classify glucose and insulin resistance status, participants underwent an oral glucose tolerance test. Insulin and glucose measures at baseline and 2 hours were used to calculate the Gutt insulin sensitivity index. This measure of insulin sensitivity is more accurate than the fasting insulin alone or the popular Homeostasis Model Assessment of Insulin Resistance (HOMA) index, which is calculated from fasting insulin and glucose concentrations and reflects predominantly hepatic insulin resistance. The Gutt index factors in postload glucose and insulin levels, which reflect, to a large degree, peripheral (ie, skeletal muscle) insulin resistance. This is important because peripheral insulin resistance is more closely aligned with vascular risk. The main outcome, ischemic stroke, was confirmed by medical record review. Participants were followed-up from enrollment in 1989/1990 to 2007 (17 years).

Risk for ischemic stroke (adjusted for age, sex, race, renal function, coronary disease, atrial fibrillation, and peripheral arterial disease) was significantly increased for persons in the fourth quartile of insulin sensitivity (ie, more insulin-resistant) compared with the first (relative risk, 1.64; 95% confidence interval, 1.24–2.16). Further adjustment for blood pressure and cholesterol attenuated the risk but it remained significant (relative risk, 1.39; 95% confidence interval,
The findings by Thacker et al are driven by the 2-hour glucose and insulin values. Fasting glucose and fasting insulin concentrations were not associated with increased risk for ischemic stroke. The greater relative importance of impaired glucose tolerance is expected, but the absence of any observed effect of impaired fasting glucose on risk for ischemic stroke is surprising. An important body of research suggests that fasting glucose in the nondiabetic range remains positively associated with vascular disease risk, including ischemic stroke specifically. The same is true for fasting insulin. Fasting and postprandial glucose and insulin levels are linked, and the variable findings from studies exploring this question may be the result of methodology rather than true biological differences. Hemoglobin A1c, which incorporates fasting and postprandial hyperglycemia, also appears to be a more robust marker of vascular risk than fasting glucose.

Although the research methods used by Thacker et al are generally sound, their results may have actually underestimated the association between insulin resistance and risk for stroke because of overadjustment in their second multivariable model. Insulin resistance can increase blood pressure through mechanisms that include upregulation of endothelin-1, microvascular dysfunction, and two properties of insulin that appear to be unimpaired in insulin resistant states, namely renal sodium retention and activation of the sympathetic nervous system. Hyperinsulinemia, especially in a hyperglycemic milieu, also increases liver triglyceride synthesis and thereby indirectly lowers high-density lipoprotein cholesterol concentrations. Hypertension and dyslipidemia, therefore, may represent intermediate mechanisms by which insulin resistance increases stroke risk; therefore, adjustment for them may attenuate the association statistically.

The article by Thacker et al is one of several studies to examine the link between insulin resistance and risk for ischemic stroke, but only the second to measure peripheral insulin resistance using more robust techniques based on glucose challenge, either with oral loading or glucose infusion. All studies have suggested an association and most report relative risks or hazard ratios at ~2.0 or more. In the context of these other studies, Thacker et al report a weaker association (relative risk, 1.64; 95% confidence interval, 1.24–2.16 in the first adjusted model), although it still reaches clinical significance. Impaired glucose tolerance also has been associated with increased risk of stroke, although the data are more scarce.

This confirmatory article by Thacker et al should lay to rest any doubt that insulin resistance and impaired glucose tolerance are important risk factors for ischemic stroke. More importantly, this work should provide new impetus to developing effective approaches to metabolic rehabilitation for prevention of first stroke and secondary prevention of vascular disease of all types in patients with a recent ischemic stroke or transient ischemic attack. Abnormal carbohydrate metabolism harms blood vessels over the course of many years. To have the greatest impact in preventing macrovascular events, metabolic rehabilitation may need to target those with the earliest manifestations (eg, obesity, insulin resistance, prediabetes).

Models for effective metabolic rehabilitation have been developed, but none is adequate for prevention of first or recurrent stroke. Cardiac rehabilitation programs typically last 12 weeks and emphasize physical activity. They have been associated with reduced all-cause mortality, but sustained effects on weight, long-term vascular outcomes, and diabetes prevention have not been demonstrated. Similarly, diet programs directed at weight loss generally produce results in the short-term, but weight is typically regained within a few months-years and the clinical significance of the resulting reduction in BMI has not been determined. Unsupervised office-based advice to increase physical activity or to lose weight is generally ineffective. For sustained weight loss, intensive programs involving personalized coaching for both fitness and nutrition, meal provision (at least initially), and continuous participation over years seem to be required.

Such intensive efforts, as exemplified by the Diabetes Prevention Program, are expensive and require a high level of commitment from participants. Even these intensive programs produce only modest weight loss over the long-term. Nevertheless, sustained multidisciplinary program-based models may be the best we have to offer in the near-term.

Because changing human behavior is difficult, pharmacotherapy and surgery are popular among patients, clinicians, and researchers. Pharmacotherapy has a second-tier role in diabetes prevention (next to lifestyle modification) and a marginal role as adjunctive therapy for weight loss. The National Institute of Neurological Disorders and Stroke (NINDS) is currently funding the Insulin Resistance Intervention After Stroke (IRIS) trial to determine the effectiveness of the insulin sensitizer, pioglitazone, in prevention of recurrent stroke and myocardial infarction among nondiabetic patients with a recent ischemic stroke or transient ischemic attack and insulin resistance (NCT 00091949). If this study proves positive, then a new avenue of clinical investigation may open. Other pharmacological agents with insulin sensitizing effects—all investigational—include other thiazolidinediones, nonthiazolidinedione Peroxisome Proliferator-Activated Receptor (PPAR) agonists, 11β-hydroxysteroid

**Figure.** A model of impaired carbohydrate regulation and its potential causal relation to ischemic stroke.
dehydroygenase-1 inhibitors, protein tyrosine phosphatase-1b inhibitors, and acetyl-coA carboxylase-1 and acetyl-coA carboxylase-2 inhibitors. For selected patients, bariatric surgery is successful in preventing progression to diabetes, but effects on vascular events and mortality remain uncertain.

Thacker et al have added to the scientific basis for a new generation of research on metabolic disease and stroke. Until these investigations bear fruit, we recommend that patients with ischemic stroke be screened for diabetes and prediabetes, and that those with abnormal findings are encouraged to enter and remain in structured programs for fitness and good nutrition.

Disclosures
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References

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The article entitled, “Metabolic Rehabilitation: Science Gathers to Support a New Intervention to Prevent Stroke,” by Kernan and Inzucchi, which published in the December 2011 issue of the journal (Stroke. 2011;42:3333–3335), included an error on page 3334. Dr. Thacker’s name was misspelled as Thatcher in 4 instances. This error has been corrected in the online version of this article.