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Screening for Diabetes after Stroke and Transient Ischemic Attack

Walter N. Kernan

Department of Internal Medicine, Yale School of Medicine,
New Haven, Conn., USA

Until recently, there were two options for type 2 diabetes screening: fasting plasma glucose (FPG) and the oral glucose tolerance test (OGTT) [1]. Elevated FPG represents primarily an increased endogenous production of glucose by the liver. Elevated 2-hour glucose by the OGTT primarily reflects impaired peripheral glucose disposal in muscle. Excessive production and impaired peripheral disposal are each cardinal features of type 2 diabetes.

In 2010, the American Diabetes Association (ADA) adopted hemoglobin A_{1c} (HbA_{1c}) as a third screening option [1]. The red blood cell membrane is highly permeable to glucose, which reacts with β -hemoglobin to form a stable glycation product (i.e. HbA_{1c}) [2]. HbA_{1c} reflects both hepatic and peripheral glucose metabolism and, therefore, may be a more synthetic measure of glucose metabolism than either FPG or the OGTT alone. Importantly, HbA_{1c} reflects the average glucose concentration over several weeks prior to testing [3]. Distinct advantages of HbA_{1c} over other measures of glycemia are: no requirement for fasting; no perturbation by acute illness or bed rest [4], and less day-to-day variation than with plasma measures of glucose [5]. It is important to note, however, that HbA_{1c} can be affected by conditions that shorten or lengthen red cell life, anemia, uremia and hemoglobin variants [3].

In this issue of *Cerebrovascular Diseases*, Fonville et al. [6] compare all three screening methods among 700 nondiabetic patients with stroke or transient ischemic attack (TIA) from a prospective registry in The Netherlands. Patients were studied an average of 4 days after their event. Prediabetes and diabetes were classified according to the current ADA guidelines, except that repeat testing was not required [1]. The results from this well-performed study are important. First, they confirm earlier work showing that the prevalence of new prediabetes and diabetes is high among patients with cerebrovascular disease and no prior diagnosis of diabetes [7]. In Fonville et al.'s study [6], 52% of the patients had newly recognized prediabetes and 27% had newly recognized diabetes, as defined by a positive finding on any one of the three screening tests.

Second, the results confirm that the OGTT classifies more patients as prediabetic and diabetic than FPG [8–10]. On a more fundamental level, the discordant results demonstrate the greater importance of impaired peripheral glucose disposal (detected by the OGTT) relative to overproduction (detected by FPG) in patients with cerebrovascular disease.

Third, the study provides new information on HbA_{1c} screening in patients with stroke and TIA: HbA_{1c} identified much fewer patients with diabetes than a single OGTT. This finding is consistent with research on nonstroke populations showing that HbA_{1c} has a sensitivity for diagnosis of diabetes of only 44% when the OGTT is used as the gold standard [10]. The importance of this reduced sensitivity was downplayed by a recent expert panel that emphasized the strong evidence that an HbA_{1c} threshold of $\geq 6.5\%$ reliably discriminated between patients at risk for microvascular complications and patients not at risk. [3] HbA_{1c} identifies more patients with prediabetes than either FBG or the OGTT.

So which test is best to screen for prediabetes and diabetes in patients with acute stroke or TIA? In the hospital, HbA_{1c} may be preferred because of the advantages cited above [3]. In newly identified diabetics, furthermore, HbA_{1c} indicates whether they reached the treatment goal ($< 7\%$) [1]. FPG is probably not adequate alone, because it will fail to identify many patients with significantly impaired peripheral glucose disposal. The OGTT will find these persons, but is cumbersome to perform. A factor in favor of the OGTT is that impaired peripheral disposal is probably more closely associated with development of cardiovascular disease compared with impaired fasting glucose [9]. Because each of the three tests provides distinct and complementary information, none should be dismissed and none can be labeled the gold standard [3]. Which-ever test is used, the classification of diabetes status requires repeat testing [1, 3, 4].

The premise of the debate on screening is that it may result in improved clinical outcome after stroke and TIA. The logic of this premise is compelling, but the data to support it are scant. Prediabetes and, more importantly, diabetes are major risk factors for first and recurrent stroke [11–13]. It has not yet been shown, however, that treatment of screen-detected prediabetes or diabetes prevents stroke [14]. What is known is that dietary modification and drugs can prevent progression from prediabetes to diabetes [15] and multifactorial management of diabetes identified by screening is associated with a small, nonsignificant reduction in the incidence of cardiovascular events and death [14]. Patients with stroke and TIA, however, are already targeted for intensive risk factor management, so the added benefit of diabetes screening for prevention of vascular events may be diminished in this population. The benefits of treating established diabetes are better documented. Multifactorial risk factor treatment for established diabetes prevents cardiovascular disease [16]. Tight control of glucose prevents microvascular disease and may prevent macrovascular events in the long run in type 1 and newly diagnosed (not screen-detected) type 2 diabetes [17, 18].

In summary, on the basis of preliminary evidence that treatment of prediabetes and diabetes may improve health after stroke, screening is reasonable and consistent with current ADA recommendations [1]. No one screening test is fully adequate, but HbA_{1c} screening is probably the best single test. For the future there is important work to be done in developing interventions to improve

clinical outcome for patients who screen positive for prediabetes or diabetes. Interventions that address the pathophysiology of diabetes (e.g. weight loss, exercise and nutrition) are obvious candidates. We have only begun to explore the therapeutic implications of data relating prediabetes and diabetes to risk for stroke.

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