Is Glycohemoglobin Testing Useful in Diabetes Mellitus? Lessons from the Diabetes Control and Complications Trial

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To address the question, Do laboratory tests cost money or save money? we have used as a model for discussion a common chronic disease, diabetes mellitus, and a widely used laboratory test, that for glycohemoglobin, a measure of long-term glycaemia used to manage diabetic patients. Diabetes mellitus is serious, highly prevalent, and costly. In 1992, $1 of every $7 spent on health in the US was for diabetes, predominantly for treatment of the chronic complications of the disease. The recently completed Diabetes Control and Complications Trial (DCCT) demonstrated that development and progression of the chronic complications of diabetes are related to the degree of altered glycaemia as quantified by determinations of glycohemoglobin. Thus, use of glycohemoglobin testing for routine diabetes care provides an objective measure of a patient’s risk for developing diabetic complications. Results of this test can alert patients and health providers to the need for change in the treatment plan. Optimal use of glycohemoglobin testing for diabetes care will require standardization of test results.

Indexing Terms: laboratory management/monitoring therapy

To address the question raised in the title of this forum, Do laboratory tests cost money or save money? we will discuss, as a model, a common chronic disease, diabetes mellitus, and a laboratory test used widely to manage diabetic patients, the test for glycohemoglobin (GHB).5

Diabetes mellitus is one of the most serious and prevalent chronic diseases worldwide. The US alone had an estimated 7.2 million diagnosed diabetic patients in 1992 (1). That same year, 47,800 workers were reported to be permanently disabled due to diabetes, 48,259 deaths were reported as caused by diabetes, and another 118,678 deaths were contributed to by diabetes. The seriousness of the condition is underscored by the fact that diabetes is the most common cause of blindness, renal failure, and limb amputation in adults.

Given the morbidity and mortality statistics, it is not surprising that the economic burden of diabetes is staggering. The direct costs of diabetes care for 1992 have been estimated at $30–40 billion. Indirect costs, including loss of time at work and loss of income to families when someone dies or cannot work, add another $40–50 billion to the estimate (1). A recent report estimated that health expenditures in the US for people with diabetes constituted about $1 of every $7 spent on health care in 1992 (2). Although the costs of routine diabetes care were significant, the largest share of the costs was related to hospitalizations for treatment of the chronic complications of the disease. Thus if it were possible to slow the onset, or better yet, to prevent the development, of diabetic complications without the need for costly new interventions, both health and cost benefits would be considerable.

What Causes Diabetic Complications?

Diabetes mellitus is characterized by insulin deficiency: absolute pancreatic deficiency of insulin in the insulin-dependent form of the condition (IDDM), and both abnormal secretion of insulin and resistance to insulin action in the noninsulin-dependent form (NIDDM). In both forms, the insulin deficiency results in hyperglycaemia (3). For many years scientists have debated whether hyperglycaemia is responsible for some or all of the chronic diabetic complications. Studies in animal models of diabetes and epidemiological studies in humans have suggested a link between hyperglycaemia and the complications. Not until the late 1970s, however, did technical advances—most notably, patient-monitored determinations of capillary blood glucose (4), GHB determinations (5), and intensified insulin regimens (6)—make it possible to conduct meaningful clinical trials. Nonetheless, the results of initial studies did not demonstrate any consistent beneficial effect of intensive therapies on diabetic complications, despite success in lowering the average concentrations of blood glucose (7–11).

The Diabetes Control and Complications Trial

In June of 1993 at the annual national meeting of the American Diabetes Association (ADA) in Las Vegas, the long-awaited results of the Diabetes Control and Complications Trial (DCCT) were reported (12, 13). This landmark study, which lasted 9 years and included 1441 patient volunteers, was designed to determine whether development and (or) progression of chronic diabetic complications could be prevented by intensive medical management in which blood glucose values were as close to the normal range as possible. Eligibility criteria included typical IDDM of duration 1 to 15 years in
subjects of ages 13 to 39 years. Patient volunteers were randomly assigned to either intensive or standard treatment groups. The standard treatment was designed to approximate conventional diabetes therapy, with one or two insulin injections per day. The intensive treatment consisted of three or more daily insulin injections or treatment with an insulin pump.

Two patient cohorts were studied to answer two different questions. The first cohort consisted of patients who had had diabetes for 1 to 5 years and who showed no evidence of diabetic retinopathy (based on seven-field stereoscopic fundus photographs); primary prevention trial. The study question in this cohort was whether intensive therapy could prevent development of retinopathy. The second cohort consisted of patients who had had diabetes for 1 to 15 years and who showed evidence of mild retinopathy at the beginning of the study. The study question in this cohort was whether intensive therapy could affect progression of early retinopathy: secondary intervention trial. Renal, neurologic, and cardiovascular outcomes were also assessed in both cohorts. Glycemic control was assessed by glycohemoglobin determinations at baseline and quarterly thereafter.

The intensive treatment group showed striking reductions in both development and progression of retinopathy, nephropathy, and neuropathy, the risk reductions ranging from ~30% to 80%. Risk reduction for all macrovascular events combined (myocardial infarction, angina, and peripheral vascular disease), was 41%, but this change was not statistically significant. The principal adverse event associated with intensive therapy was a threefold increase in severe hypoglycemia.

On the basis of these findings, the study group recommended that most patients with IDDM be treated with intensive regimens, with a goal of maintaining blood glucose concentrations as close to the normal range as safely possible. No specific recommendations were made regarding treatment of IDDM patients younger or older than the study cohort or of persons with NIDDM.

After announcement of the DCCT results, the ADA recommended in a position statement that most patients—both those with IDDM and NIDDM—should strive to achieve blood glucose concentrations as close to the normal range as possible, but with individualization of specific goals (14). The ADA statement noted that costs of intensive therapy are greater than current conventional therapy and “hoped that the long-term benefits of healthier more productive lives with fewer complications will offset the costs of tight control.” Preliminary studies by the DCCT Study Group suggest that costs of intensive therapies as they would probably be applied in the general community are about double the costs of current conventional therapies (unpublished data from the Centers for Disease Control, W. Herman, June 13, 1983). Most of the increase in costs is related to increased frequency of clinic visits and home blood glucose testing and to costs of increasing the availability of specialized diabetes education centers. However, the increased costs of intensive therapies are also estimated to be offset by savings from reduced frequency of complications. For example, in the DCCT, intensive therapy decreased by 50% the need for laser surgery for proliferative retinopathy, a vision-threatening form of diabetic eye disease.

GHB Testing in the DCCT

What do the DCCT results have to do with GHB testing, the main subject of this presentation? The GHB test is a simple blood test that quantifies hemoglobin—glucose adducts formed by nonenzymatic glycation (15). The test has been available for routine clinical use since the late 1970s, and the amount of GHB in blood is considered an accurate index of the mean blood glucose concentration during the preceding 4 months. The DCCT results showed that glycemic control, as estimated by GHB determinations, is linked closely to a diabetic patient’s risk of developing chronic diabetic complications of the eyes, kidneys, peripheral nerves, and perhaps heart and blood vessels. Within 6 months after initiation of the trial, GHB levels fell by ~2 percentage points in the intensive treatment group, compared with no change from baseline in the conventional treatment group. Mean GHB concentrations (percent of total hemoglobin) in the intensive and conventional treatment groups were ~7% and 9%, respectively; the range in nondiabetics was 4–6%. The difference in GHB values between the treatment groups was maintained for the duration of the trial and reflects a decrease in mean blood glucose of ~3.33 mmol/L (~60 mg/dL), from ~11.6 to 8.33 mmol/L (~210 to 150 mg/dL). However, there was a strong inverse relationship between GHB and risk of severe hypoglycemia; the closer to normal the GHB value was, the greater was the risk of hypoglycemia.

Implications of the DCCT Results for GHB Testing

The DCCT results provide strong evidence that glycemic control as assessed by GHB testing predicts risk for developing diabetic complications. For a test to be cost-effective, however, it is not enough that it predicts risk. The cost of doing the test might not be justified unless the test provided information that potentially could improve outcome. Logically, knowing that a patient’s GHB was high would help the patient and health providers make changes in treatment that would lower the GHB, thereby decreasing risks of complications. Larsen et al. (16) recently tested this assumption. They assigned 240 patients with IDDM randomly to either a treatment or a control group. Both groups received GHB testing quarterly for 12 months; however, test results were made available to study patients and health providers only in the treatment group. There were no other specific differences in management between the two study groups. After 1 year, GHB values were substantially lower in the treatment group than in the control group. The greater the GHB level at baseline, the greater its decrease after 12 months. These data, taken together with the DCCT results, argue strongly for the use of GHB testing on a routine basis: GHB testing apparently helps to lower GHB results, and the lower the GHB, the less the risk of diabetic complications.
Even before the DCCT results were published, the ADA had recommended (17) that GHB testing be performed at the initial assessment and that therapy for diabetes be instituted; thereafter, GHB testing was recommended semi-annually in persons with NIDDM, quarterly in persons with IDDM, and more frequently in all persons with poorly controlled diabetes. Despite these widely published recommendations, it is estimated that only ~25% of patients with diabetes have GHB testing performed on a regular basis (unpublished data from Bio-Rad, Inc., Genrikh Sivorinovskiy, June 10, 1993). Why compliance with the ADA recommendations has been so low is not clear; perhaps uncertainty by health providers as to a link between glycemic status and diabetic complications is a factor. Other possible reasons include cost of the test (an informal survey conducted by our laboratory in November 1993 found that costs per test varied from about $12.00 to $50.00), lack of knowledge about the test by the health provider and the patient, and uncertainty of the health provider regarding the potential therapeutic benefits of knowing the test result.

With the wide publicity given the DCCT results, we predict that routine GHB testing volume will increase dramatically. The recent proliferation of new GHB testing methods suggests to us that manufacturers must have anticipated the outcome of the DCCT and its impact on diabetes care. We believe there will be strong pressure from health providers and patients to standardize GHB test results (18); at present, however, there is no consensus on a GHB reference material or a reference method. GHB values generated in one laboratory cannot be compared directly with those in another laboratory, even if both use the same assay method. Fortunately, recent studies demonstrate clearly the feasibility of standardizing test results among a wide variety of assay methods (19–22). Standardization of test results to DCCT numbers would be particularly attractive given that the DCCT GHB values predict the risk of diabetic complications. In addition, data from the DCCT were used to establish a relationship between GHB value and mean blood glucose concentration, a task that would be extremely difficult for most laboratories to do independently for each method. Recognizing the need to standardize GHB test results, in 1992 the Standardization Committee of the AACC formed a subcommittee to develop and implement a GHB standardization program.

Standardization of GHB assay results might open some new doors for the test. Because GHB values define risk for diabetic complications, use of the test for diabetes screening and even for diagnosis will need to be considered seriously. Epidemiologic studies show that many cases of diabetes in the US are undiagnosed—perhaps as many are undiagnosed as diagnosed. Diagnosing diabetes at an early stage and treating the condition to maintain blood glucose concentrations as close to the normal range as possible is preferable to making a diagnosis after a person has had high blood glucose and high GHB for several years without any symptoms but now presents with far-advanced complications. This scenario is, unfortunately, a common one. GHB testing could be used to identify individuals at increased risk for developing diabetic complications (23, 24).

Now that the US plans to make major changes in its healthcare system, with cost containment a driving force, all aspects of healthcare will be scrutinized closely. Although the costs of laboratory testing represent only a very small percentage of total health care expenditures, they will be an easy target for reductions. One will have to justify not only the cost of performing a test, but also the need for the test. The process will be difficult and will require close cooperation between clinicians and laboratorians, but if performed properly, costs will be decreased and patient care will not be compromised. Some of the cost savings will not be realized immediately but will show up only in the long run, as improved outcomes. This concept of “pay a little now and save a lot later,” is something the cost-cutters will need to consider carefully in their cost–benefit assessments. Diabetes mellitus is a good example; the costs of increased GHB testing and costs of other aspects of intensive therapy should be offset by much larger savings in other areas, such as decreased need for such major expenditures as laser therapy, kidney dialysis, and renal transplantation. Thus, a small investment could generate a very large return.

References