HbA_{1c} May Soon Be Top Diabetes Diagnostic Test

BY MITCHEL L. ZOLER

The way that diabetes is diagnosed in the United States is about to change.

Later this year, an expert panel organized by the American Diabetes Association will issue a report making blood level of glycosylated hemoglobin (HbA_{1c}) an accepted method for diagnosing diabetes, according to staffers from the ADA. Although the decision is not yet finalized, "the group will likely recommend [HbA_{1c}] as the preferred test," placing it above the current diagnostic standard (the fasting blood glucose level) and also above the historic criterion for diabetes diagnosis (the glucose tolerance test), said Dr. Sue Kirkman, the ADA's vice president for clinical affairs.

The report from the ADA's Expert Committee on the Diagnosis and Classification of Diabetes will also set the HbA_{1c} cut point for diagnosing diabetes, but this value has not yet been finalized.

This shift on the use of HbA_{1c} for diagnosis stands to legitimize the method that is already commonly used by many primary care physicians, said Dr. Mayer B. Davidson, an endocrinologist at Charles R. Drew University of Medicine and Science in Los Angeles and professor of medicine at the University of California, Los Angeles. He applauded the decision, noting that "HbA_{1c} is a more valid way to look at what is going on with glucose," compared with glycemia levels.

Adoption of HbA_{1c} as the primary diagnostic method also stands to make the diagnosis of diabetes substantially easier than it has been up to now, meaning that more people will probably be tested and thus more people with the disease will be identified.

"Since the HbA_{1c} test doesn't require fasting, the hope is that it will be more convenient and that more people will get tested and diagnosed early," Dr. Kirkman said in an interview, noting that an estimated 25% of people in the United States who have diabetes are undiagnosed.

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DR. KIRKMAN

The Expert Committee on the Diagnosis and Classification of Diabetes is an ad hoc group that the ADA convenes when it "feels there is a need to revisit some area related to diagnosis or classification," Dr. Kirkman said.

The current round of deliberations began last year, and the group was constituted not only with members picked by the ADA, but also with representatives from the European Association for the Study of Diabetes and the International Diabetes Federation. "Eventually it is hoped that all three organizations will adopt the recommendations so that there is a worldwide standard." ADA officials think the report may be ready for release before or during the ADA's annual scientific sessions in June.

Making HbA_{1c} an accepted diagnostic test—let alone the preferred test—has been on the table for years. In a recent talk at a meeting sponsored by the ADA in New York, Dr. William C. Knowler spelled out the case in favor of using glycosylated hemoglobin, as well as the shortcomings of this approach.

The strengths of HbA_{1c} as a diagnostic tool include the following:

► A more standardized assay and substantially less interlaboratory variability, compared with measurements of blood glucose.

► Consistency in using the same assay for diagnosis that is also routinely used to monitor patient treatment and to predict the risk for long-term complications.

► A better index of overall glycemia.

► No need for fasting before the specimen is drawn.

► No effect from acute changes in levels of blood glucose, such as those caused by illness.

Another attraction of HbA_{1c} is that when the level goes above 7.0%, it becomes strongly correlated with the development of microvascular complications, noted Dr. Davidson. "There is no absolute way to diagnose" diabetes. "Where we draw the line is somewhat arbitrary." Basing diagnosis on a test that can reliably predict the risk for microvascular complications is attractive because these complications "are fairly specific to diabetes," he said in an interview.

But relying on HbA_{1c} for diagnosis also has limitations. A person's HbA_{1c} level can be affected by hemoglobinopathies, variations in red cell turnover, and unexplained racial differences, said Dr. Knowler, chief of the Diabetes Epidemiology and Clinical Research Section of the National Institute of Diabetes and Digestive and Kidney Diseases in Phoenix and a member of the Expert Committee.

Perhaps most importantly, switching the diagnostic criterion will create a break from the past that might make it hard to reconcile old epidemiologic observations with new ones.

A similar break occurred in 1997, when the ADA switched its diagnostic standard from the blood glucose level 2 hours following an oral glucose challenge to a fasting blood glucose level. That switch resulted in a sudden spike in the number of patients diagnosed with diabetes, Dr. Knowler said.

The fact that an HbA_{1c} cut point for diagnosis has still not been set highlights the controversy this issue generates. A cut point of 6.5% has "some useful properties," he acknowledged, but 5.5% is "a level to raise concern" that a person is at risk for eventually developing diabetes. Choosing a cut point "is a complicated issue that depends on how harmful are missed diagnoses and overdiagnosis," he said.

In contrast, Dr. Davidson, who is not a member of the current Expert Committee although he served on it in the past, leans toward a cut point of 7.0% because of its significance for microvascular disease. ■

Thiazolidinedione Use Linked to Increased Fracture Risk

BY MITCHEL L. ZOLER

NEW YORK — Treatment with a thiazolidinedione, either pioglitazone or rosiglitazone, has been linked to an increased rate of bone fractures, particularly in women, in several recently published reports.

Although a definitive link between these drugs and an increased fracture risk has not yet been proved, the evidence amassed so far is suggestive enough to prompt caution in the treatment of patients with a thiazolidinedione (TZD), Dr. Robert G. Josse said at a meeting sponsored by the American Diabetes Association.

"In those with a higher fracture risk, consider other hypoglycemic therapy," advised Dr. Josse, professor of medicine and nutritional sciences at the University of Toronto and medical director of the department of medicine at the osteoporosis center at St. Michael's Hospital in Toronto.

In addition, "if using a TZD, consider therapy to prevent TZD-induced osteoporosis." Standard therapies for osteoporosis are effective in patients with diabetes—including those with diabetes who develop steroid-induced osteoporosis—but no data now exist on the efficacy of antiosteoporosis treatments for countering the possible effects of TZDs, he noted.

In one recent meta-analysis, patients treated with a TZD had a 45% increased risk for bone fracture.

DR. JOSSE

Reasonable steps to reduce the fracture risk in patients who must take a TZD include optimizing calcium intake and the supply of vitamin D, encouraging adequate exercise, and taking precautions to prevent falls. Administration of antiresorptive drugs, such as raloxifene and the bisphosphonates, seems to be effective in patients with diabetes, but the effects of bone anabolic drugs such as teriparatide in these patients isn't known.

The idea that treatment with pioglitazone (Actos) or rosiglitazone (Avandia) may cause osteoporosis and produce an increased rate of bone fractures is biologically plausible, and has been suggested in the results from adverse-event reports from several studies.

Perhaps the most persuasive evidence so far is a meta-analysis published in January that compiled adverse-event data from 10 randomized, controlled studies with a total of more than 13,000 patients, and also reviewed two observational studies with a total of more than 31,000 patients (CMAJ 2009;180:32-9). In the 10 randomized trials, patients treated with a TZD had a statistically significant 45% increased risk for bone fracture, compared with patients in the control groups.

When the analysis broke the study population down by gender, a statistically significant 2.2-fold increased fracture risk was seen in women treated with a TZD, but absolutely no increased risk was seen in men. Additional analysis by sex showed that, in women, TZD treatment was linked with significant reductions of bone mineral density in the lumbar spine and hip. The two observational studies also showed a significant link between TZD use and fracture risk in women, but not in men.

The two short-term, randomized studies included a study with 50 healthy postmenopausal women without osteoporosis or diabetes who were randomized to treatment with 8 mg rosiglitazone daily or placebo for 14 weeks. Despite the brief period of treatment, the women in the rosiglitazone-treated group had a statistically significant reduction in their total hip bone mineral density, compared with the placebo group (J. Clin. Endrocrinol. Metab. 2007;92:1305-10).

A second study, published last May, randomized 30 postmenopausal women with polycystic ovary syndrome but without diabetes to treatment with either 30 mg pioglitazone daily or placebo. After 16 weeks, the women treated with pioglitazone had significantly lower lumbar spine and femoral neck density, compared with the controls (J. Clin. Endrocrinol. Metab. 2008;93:1696-701). The TZD-treated women also showed significantly decreased blood levels of bone-turnover hormones and enzymes.

Dr. Josse reported receiving research support from, and serving on the speakers bureau and advisory panel for, several companies including Amgen Inc., Eli Lilly & Co., Procter & Gamble Co., and Sanofi-Aventis. ■