

Data Conflicting on Depression-Diabetes Link

BY JEFF EVANS
Senior Writer

WASHINGTON — Which comes first, diabetes or depression?

The data on this temporal relationship are mixed. While findings from previous studies suggest that depression precedes diabetes, findings from another investigation, presented at the annual scientific sessions of the American Diabetes Association, propose that no time correlation exists between the two diagnoses.

This chicken-or-egg question is important because depression has a reported prevalence ranging from 11% to 33% in patients with diabetes, which is twice as high as it is in people without diabetes, said Dr. Lawrence S. Phillips, professor of medicine in the division of endocrinology and metabolism at Emory University, Atlanta.

Dr. Phillips and his colleagues conducted a cross-sectional study of 573 people (about half were white and half were African American) who said that they did not have diabetes. Each person received a 75-g oral glucose tolerance test after an 8-hour overnight fast, and screening for depression with a well-validated tool, the Patient Health Questionnaire.

Normal glucose tolerance (NGT) occurred in 65% of the participants while 15% had impaired fasting glucose (IFG), 8% had impaired glucose tolerance (IGT), 8% had both IFG and IGT, and 4% had diabetes. Some participants had received

(11%) or were currently receiving (12%) treatment for depression.

PHQ scores rose in a statistically significant trend from being low among those who never underwent treatment for depression to being higher in people who received depression treatment in the past and highest in individuals who were currently receiving depression treatment.

But there was no relationship between the different categories of glucose tolerance and PHQ score, the prevalence of any depressive syndrome or major depressive disorder, or the severity of depression, Dr. Phillips said.

In multivariate analyses, higher body mass index and current receipt of depression treatment significantly increased the risk of having any depressive syndrome, but this risk was not increased within any category of glucose tolerance.

One audience member asked Dr. Phillips how he viewed the results of his study in light of the fact that a poster presented at last year's ADA meeting found that patients with IGT in the Diabetes Prevention Program had a significantly increased risk for depression, suggesting depression may have preceded IGT.

"It's certainly possible that among people who are depressed, there are neuroendocrine changes that lead to diabetes. There's certainly room in human biology for both processes," Dr. Phillips said.

But he argued that the situation in which depression precedes the development of diabetes is unlikely given the lack

of an association between depression and unrecognized IGT in his study and the fact that patients in the Diabetes Prevention Program were told that they had IGT and were at risk for diabetes, which could possibly have had a negative psychosocial effect.

Firm conclusions favoring either side of the issue, however, may have to wait for research into the dynamics of neurohormonal changes, which are believed to underlie some of the association between depression and the development of diabetes, said Dr. Sherita Hill Golden of the division of endocrinology and metabolism at Johns Hopkins University, Baltimore.

Melancholic depression is known to increase the activation of the hypothalamic pituitary adrenal (HPA) axis, which leads to a simultaneous activation of the sympathetic nervous system, Dr. Golden said.

In the tightly regulated feedback loop of the HPA axis, the hypothalamus produces corticotropin-releasing hormone (CRH) that stimulates the pituitary gland to release adrenocorticotropin hormone (ACTH), which stimulates the adrenal gland to release cortisol. Cortisol levels then in turn regulate the production and release of CRH.

There is evidence to suggest that subclinical hypercortisolism, defined as having two of three abnormalities in HPA axis function (increased 24-hour urine free cortisol, failure of the dexamethasone suppression test, and decreased levels of ACTH), may contribute to the develop-

ment of type 2 diabetes, Dr. Golden said.

One study of 12 patients with adrenal incidentalomas and subclinical hypercortisolism found that such patients had a higher prevalence of insulin resistance, impaired glucose tolerance, and type 2 diabetes, as well as greater central adiposity, than did 29 patients with a nonfunctioning adrenal incidentaloma and no subclinical hypercortisolism (*J. Clin. Endocrinol. Metab.* 2002;87:998-1003).

Dr. Golden's own research has centered on determining which measures of neuroendocrine activity provide the most reliable results, and understanding how that activity correlates with metabolic parameters. Preliminary results of an extensive 3-day series of tests in 15 healthy African American women have indicated that static measures of HPA axis activity, such as salivary cortisol sampling, do not correlate well with more dynamic measurements, such as 24-hour urine-free cortisol levels. Other analyses in the patient group suggested that CT scan measurements of adrenal gland volume and the results of dexamethasone suppression testing are correlated strongly with body mass index, high-density lipoprotein cholesterol, and systolic blood pressure.

The results of studies measuring the effect of neuroendocrine changes on metabolic parameters are beginning to suggest that "modification of the neurohormonal response may provide a novel approach to the primary prevention of type 2 diabetes," Dr. Golden said. ■

Cognition Is Not Impaired by Intensive Glycemic Control

BY JEFF EVANS
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WASHINGTON — Tight glycemic control early in the course of type 1 diabetes does not result in later cognitive decline, according to new findings from two studies with an average of 18 years of follow-up data.

"Because of the length of follow-up and extent of cognitive testing, this study strongly supports the safety of intensive diabetes therapy," Dr. Alan M. Jacobson said at the annual scientific sessions of the American Diabetes Association.

The results should allay the serious concerns that have been raised about whether tight glycemic control might lead to more severe hypoglycemic episodes and subsequent decreased cognitive ability, said Dr. Jacobson, head of the behavioral and mental health research section at the Joslin Diabetes Center, Boston.

But the recurrent, severe hypoglycemic events that are more likely to occur with tight glycemic control could still possibly have a negative cognitive effect on older adults, very young children, or those with a longer disease duration, he added.

The results from the multicenter, randomized Diabetes Control and Complications Trial (DCCT) and its continuation in the long-term observational Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that patients

who received intensive glycemic control during the DCCT did not have any differences in cognition, compared with conventional treatment, as measured by an extensive test battery involving eight cognitive domains (problem solving, learning, immediate memory, delayed recall, spatial information, attention, psychomotor efficiency, and motor speed), Dr. Jacobson reported.

The 18 years of combined follow-up make the DCCT and the EDIC the largest, longest-term prospective study that has implemented a cognitive assessment of patients with any clinical condition, he said.

Among patients in either group, there were no differences in cognitive functioning in those who had no hypoglycemic episodes, one to five episodes, or more than five episodes.

Control of HbA_{1c} (glycosylated hemoglobin) values to less than 7.9% similarly showed no significant effects, except in sparing patients from small reductions in psychomotor efficiency and in improving motor speed. The "very modest" declines in psychomotor efficiency and motor speed that were associated with higher HbA_{1c} values (7.9% or greater) were "consistent with emerging literature on the ef-

fects of persistent hyperglycemia on mental and motor slowing," Dr. Jacobson said.

The results did not change when the investigators removed 28 patients with potentially confounding illnesses—strokes, decreased vision, renal insufficiency—from the analysis, except that patients who had prior tight glycemic control in the DCCT had a significantly lower decline in

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psychomotor efficiency than did patients who received conventional treatment.

All of the analyses were adjusted to account for the confounding variables of baseline age, gender, years of education, length of follow-up, and the number of cognitive tests taken. (Patients took different numbers of tests because they entered the DCCT at different times.)

The initial results at the end of the DCCT showed that maintenance of near normal glycemic control reduced the risk of developing—or the progression of—microvascular complications.

After 10 years of additional follow-up in the EDIC study, the patients who had prior intensive treatment still had reduced progression of retinopathy, nephropathy, neuropathy, and cardiovascular events.

As patients in the intensive treatment

arm of the DCCT finished the trial and entered the EDIC study, they did not maintain the same level of glycemic control during the ensuing years, whereas individuals who were in the conventional treatment arm of the DCCT received training on how to maintain tight glycemic control and soon began doing so on their own. Both groups had a mean HbA_{1c} value of 7.8% at the end of 12 years of follow-up in the EDIC study, which includes more than 90% of the original DCCT patients.

At the end of those 12 years, a significantly greater percentage of the 583 patients who were in the intensive treatment arm of the DCCT had one or more severe hypoglycemic events leading to coma or seizures than did the 553 patients who received conventional treatment (44%, or 258 patients with 880 events, vs. 34%, or 187 patients with 452 events).

Most (97%) of the participants were white and were 27 years old on average when they entered the DCCT, where they received a mean of 6.5 years of intervention; they were 45 years old on average after 12 years of follow-up in the EDIC trial. At the last follow-up, all of the participants were adults and about 50% were employed as professionals.

The patients in the study were "unusually healthy and subject to careful follow-up, which may suggest that those in worse control may show worse cognitive outcomes," he said. ■