Extremes in HbA_{1c} Levels Linked to Dementia Risk

Dementia risks increased when HbA_{1c} values reached 12% and higher and when they fell below 5%.

BY DENISE NAPOLI
Assistant Editor

CHICAGO — Excessively high and extremely low levels of glycosylated hemoglobin were associated with an increased risk for dementia in elderly patients with type 2 diabetes, according to the findings of a cohort study involving more than 22,000 patients.

Dr. Rachel Whitmer surveyed a cohort of 22,852 patients older than age 55 from the Kaiser Permanente Northern California diabetes registry who had their HbA_{1c} measured at least once between 1994 and 1996, and checked these same patients' records again between Jan. 1, 1997, and May 30, 2006, for a diagnosis of dementia, vascular dementia, or Alzheimer's disease. People who had a prior diagnosis of dementia at the initial survey were excluded from the study.

In presenting the data at the annual meeting of the American Academy of Neurology, Dr. Whitmer described the cohort, which was 48% female and 35% nonwhite, as a "very diverse sample." The mean age at the time of the initial survey was 65 years.

A total of 2,488 participants (11%) were diagnosed with dementia during the follow-up period. Patients with dementia were more likely to be on insulin and have had a longer duration of diabetes than were those without dementia, said Dr. Whitmer, an investigator at the division of research, Kaiser Permanente Northern California.

The researchers used a reference glycosylated hemoglobin level of 7%, because this is the cutoff point that endocrinologists aim for to lower the risks of complications.

Surprisingly, "we really did not see an elevated risk of dementia until we got to values that were from 10% to 11.9% and really 12% or greater," she said.

Diabetes patients with HbA_{1c} values of 15% and above were 83% more likely to receive a diagnosis of dementia during the follow-up period than were their diabetic peers with glycosylated hemoglobin levels under 7%.

Diabetics with values of 12% or more had a 22% elevated risk of dementia.

However, the investigators also looked at people with extremely low levels of HbA_{1c}—less than 5%—and found that this group actually had the greatest risk of dementia. People with levels less than 5% were 2.2 times more likely to have dementia, compared with patients with levels between 5% and 7%.

All risk assessments were made after adjusting for age, education, race, sex, weight, treatment, diabetes duration, hypertension, hyperlipidemia, heart disease, and stroke.

"Most endocrinologists like to aim for [HbA_{1c}] levels less than 8% or less than 7%," said Dr. Whitmer. "It's been shown that this lowers the risk of stroke and hypertension." However, physicians would do well to take into account these new cutoff points for dementia risk in their assessment of patients. "When we're looking at elderly people with diabetes, overcontrol can be just as much as a problem as not as much control," Dr. Whitmer said.

One of the study's limitations is that HbA_{1c} might have been underestimated for those patients whose dementia went undiagnosed. Furthermore, no brain imaging or cognitive tests were available to confirm the dementia diagnoses. Future studies are needed to confirm the findings.

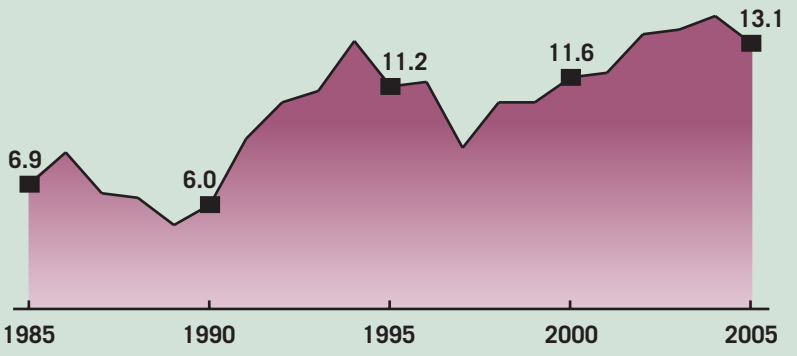
It's unknown what the mechanism would be that links HbA_{1c} and dementia, added Dr. Whitmer.

Dr. Whitmer reported no disclosures in relation to her presentation. One of her fellow researchers on this study disclosed relationships to Novartis Corp., Myriad Genetics Inc., and Posit Science.

DATA WATCH

Incidence of Diabetes in Elderly Almost Doubled In the Last 2 Decades

(per 1,000 population aged 65-79 years)



Source: Centers for Disease Control and Prevention

Adverse Event Patterns Differ

Pioglitazone *from page 1*

a baseline HbA_{1c} of 6%-9%.

HbA_{1c} levels fell in both treatment groups, although pioglitazone produced a significant and more sustained benefit, Dr. Nissen said. The mean difference in HbA_{1c} was small, 0.19%, favoring pioglitazone.

Significant differences in systolic and diastolic blood pressure were observed, favoring pioglitazone, he said. Systolic BP increased 2.3 mm/Hg in the glimepiride group and was unchanged in the pioglitazone group, a significant difference. Diastolic pressure rose 0.9 mm Hg in the glimepiride group and fell 0.9 mm Hg in the pioglitazone group.

In terms of biochemical parameters, pioglitazone patients showed significant improvements in HDL cholesterol, compared with glimepiride patients, with increases of 16% and 4%, respectively; high-sensitivity C-reactive protein, with decreases of 45% and 18%; and triglycerides, which fell 15.3% with pioglitazone treatment and rose 0.6% with glimepiride. LDL cholesterol rose slightly in the glimepiride patients, but there was no significant difference between groups.

Although the trial was not powered to assess major cardiovascular events, an adjudicated composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke occurred in 2.2% of the glimepiride patients and 1.9% of the pioglitazone patients. Noncardiovascular death occurred in 0.4% and 0% and coronary revascularization in 11% and 10.7%. Owing to the small size of the trial, none of these differences approached statistical significance, he said.

Both regimens were well tolerated, but revealed a different pattern of adverse events. Events that were significantly higher in the glimepiride group than the pioglitazone group were hypoglycemia (37% vs. 15%, respectively) and angina (12% vs. 7%). Those that were more frequent in the pioglitazone group than the glimepiride group were edema (11% vs. 18%), bone fractures (0% vs. 3%, respectively), and weight gain (1.6 kg vs. 3.6 kg), said Dr. Nissen, who disclosed relationships with AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Co., Hoffmann-La Roche Inc., Pfizer Inc., Eli Lilly & Co., Sanofi-Aventis U.S. LLC, Takeda Pharmaceutical Co., Novartis Pharmaceuticals Corp., Prevention/Vascular, and I-Significant.

Baseline characteristics evaluated were similar between the pioglitazone (n = 270) and glimepiride (n = 273) groups, in regards to age (mean 60 years), diabetes duration (6 years), and body mass index (32 kg/m^2). Significantly more patients in the glimepiride group had hypertension (92% vs. 83%) and were current smokers (19% vs. 11.5%).

Discussant Dr. B. Greg Brown, professor of medicine at the University of Washington, Seattle, said, "We don't know for sure that there are clinical benefits associated with this improvement in stenosis severity, but the trends look favorable."

He then asked Dr. Nissen if the findings have changed his opinion regarding the glitazone class of drugs.

Dr. Nissen responded that the two available drugs—rosiglitazone and pioglitazone—have very different effects in terms of their lipid effects, with rosiglitazone raising LDL by 18%-20% and pioglitazone having very little effect. Moreover, while both drugs target the gene that lowers blood sugar, they otherwise have extraordinarily different effects. "We have to study each of these compounds individually," he said. "Many drugs in this class have failed due to toxicity because their genetic effects are unpredictable.

'The cardiovascular benefit with pioglitazone comes along with an increased risk of heart failure, bone fractures, weight gain, and edema.'

"I think what happened here is that pioglitazone has the right constellation of effects to produce a beneficial effect, whereas rosiglitazone clearly produces harm," he said.

Dr. John M. Flack lauded the rigorously performed trial, saying it "provided further evidence of the potential cardiovascular benefits of pioglitazone for cardiovascular risk reduction," but noted that pioglitazone is not without its own risks. "Practitioners should remember that using most drugs, including pioglitazone, represents an assessment of benefits versus risk. The cardiovascular benefit with pioglitazone comes along with an increased risk of heart failure, bone fractures, weight gain, and edema," said Dr. Flack, chair of the department of medicine and chief of translational research and clinical epidemiology at Wayne State University, Detroit, in an interview. "On the other hand, diabetes management will typically require multiple hypoglycemic agents and in appropriately selected patients practitioners should feel reassured about the favorable cardiovascular risk profile of pioglitazone," he added.

When asked why metformin was not used in the trial, Dr. Nissen replied that the two drugs were chosen because they work by "diametrically opposed mechanisms," Dr. Nissen said in a press conference. "We wanted to test an insulin providing therapy [glimepiride] against an insulin sensitizing therapy [pioglitazone]."

The most important message of PERISCOPE is that comparative effectiveness trials must be performed in all diabetes treatment strategies, he continued. "We can't just focus on pricking the finger, getting the blood sugar down, and saying that's the goal of therapy. The goal of therapy is to prevent the complications of diabetes. And the most serious complication is heart disease."

Pages 12a—12b