# DHA Findings Too Weak to Back Use in AD

BY MICHELE G. SULLIVAN

VIENNA — Docosahexaenoic acid might improve memory in elderly subjects with mild memory complaints, but the nutritional supplement has no beneficial effect in those with Alzheimer's disease, two randomized, placebo-controlled trials have determined.

Although docosahexaenoic acid (DHA) did slow cognitive decline in a subset of Alzheimer's patients who carried the ApoE4 gene, the nonsignificant finding is not enough to recommend the supplement as a possible therapy, Dr. Joseph F. Quinn said at the International Conference on Alzheimer's Disease. "This is an intriguing exploratory result," said Dr. Quinn, primary investigator of the National Institute on Aging–supported trial. "However, it must be treated with appropriate caution." Overall, he said, "these results do not support the routine use of DHA for patients with Alzheimer's."

The second study, which examined DHA's effect on memory performance in normal subjects with mild, age-related memory difficulties, concluded that the supplement did significantly improve performance on a memory test. This finding suggests that DHA may offer some benefit very early in the disease process, said Dr. Marwan Sabbagh, director of clinical research at the Sun Health Research Institute, Sun City, Ariz.

"The data suggest that DHA may serve to reduce risk by perhaps facilitating neuronal health," Dr. Sabbagh said in an interview. "However, it appears that once symptomatic Alzheimer's is present, the critical mass of pathology may be too much for even DHA to offset."

Dr. Samuel Gandy, the Mount Sinai Professor of Alzheimer's Disease Research at the Mount Sinai School of Medicine, New York, agreed. "I would conclude that there is no consensus indicating any obvious meaningful benefit," for DHA treatment in Alzheimer's, he said in an interview.

The federally sponsored DHA trial in Alzheimer's patients was part of the national Alzheimer's Disease Cooperative Study. Dr. Quinn, of the Oregon Health & Science University, Portland, and his colleagues conducted a randomized, placebo-controlled trial that comprised 402 patients with mild to moderate Alzheimer's; they were randomized to either placebo or 2 g DHA per day for 18 months.

The patients' mean age was 76 years; their mean score on the Mini-Mental State Exam (MMSE) was 21. Almost 60% were positive for the ApoE4 gene. Primary outcomes were changes in the MMSE, the Alzheimer's disease Assessment Scale-cognitive domain (ADAS-cog), the Clinical Dementia Rating (CDR), and the Nurse Psychiatric Inventory (NPI).

"Although DHA had a modest benefit on the ADAS-cog score compared to placebo at 12 months, there was no significant difference between the two by the end of the study," Dr. Quinn said. "If you compared the scores at 12 months, they were statistically significantly different, but that was not a planned finding so it's nothing we can hang our hats on."

Both the CDR and ADAS-cog scores showed sharp, linear declines that were virtually identical in both groups. There were no significant differences in either the MMSE or NPI scores at the end of the trial.

When the group was stratified by ApoE4 status, the researchers did identify a trend toward a slower rate of decline on both the MMSE and ADAS-cog among ApoE4-negative patients taking DHA. "It appears that there was some effect in the treatment group," Dr. Quinn said. "However, we have to remember that this analysis is a preliminary finding, and we don't think it's likely to hold up after adjustment" for possible confounding factors.

The second trial was sponsored by Martek Biosciences Corp. of Columbia, Md. Karin Yurko-Mauro, Ph.D., and her colleagues randomized 485 healthy older people with mild memory complaint to either placebo or 900 mg/day DHA. The primary outcome measure was a change from baseline on the CANTAB Paired Associate Learning (PAL), a visuo spatial episodic memory test.

At baseline, the subjects' mean age was 70 years; they had a mean of 15 years of education. Most (84%) were white. The mean baseline MMSE was 28.

After 18 months of therapy, subjects taking DHA performed significantly better on the PAL than those taking placebo. The DHA group made an average of four fewer errors on the PAL than they did at baseline, while those taking placebo made an average of two fewer errors on the subsequent test—a significant difference. "The benefit is roughly equivalent to having the learning and memory skills of someone 3 years younger," Dr. Yurko-Mauro said.

Patients taking DHA also experienced a significant decrease in heart rate from baseline of three fewer beats per minute, while those taking placebo experienced a decrease of just one beat per minute. Blood pressure and body weight were unchanged in both groups. There were no treatment-related adverse events.

Dr. Yurko-Mauro is the associate director of clinical studies at Martek Biosciences, which sponsored the study; Dr. Quinn reported no potential conflict of interest.

The meeting was sponsored by the Alzheimer's Association. ■

# Severe Hypoglycemia Raises Dementia Risk in Type 2 Elderly

BY MIRIAM E. TUCKER

WASHINGTON — A history of severe hypoglycemic episodes was associated with an increased risk for dementia in a longitudinal cohort study involving 16,667 older patients with type 2 diabetes.

"Severe hypoglycemic episodes might be associated with a neurological consequence in a population that is already at greater risk for dementia. …This study also adds to the evidence base that balance of glycemic control is a critical issue, particularly for the elderly," Rachel A. Whitmer, Ph.D., said at a press briefing timed to coincide with publication of the special diabetes edition of the Journal of the American Medical Association.

The study, which retrospectively analyzed data from the Kaiser Permanente Northern California Diabetes Registry, identified a 2.39% increase in absolute risk of dementia per year of follow-up for patients with a history of hypoglycemia that resulted in hospitalization or an emergency department visit, compared with type 2 diabetic patients without such a history.

"Trying to aim for a very low glycemic target might not be beneficial and might even be harmful. We know that high blood sugar isn't good, but I think the message here is also that very low levels aren't good," added Dr. Whitmer of Kaiser Permanente's division of research.

Because the data analyses included two methods by which the hypoglycemia events were separated in time from the onset of dementia, the study supports the direction of causality that the hypoglycemia preceded the dementia, rather than the other way around. Moreover, "Our findings were independent of glycemic control as assessed by levels of [hemoglobin $A_{1c}$], type of diabetes treatment, and diabetes comorbidities," wrote Dr. Whitmer and her associates in the published report (JAMA 2009;301:1565-72).

The patients were all aged 55 or older on Jan. 1, 2003, with no signs of dementia at that time. A total of 11% (1,822) patients were diagnosed with dementia during a mean follow-up of 3.8 years and a median follow-up of 4.8 years, and a total of 8.8% (1,465) had at least one episode of severe hypoglycemia during 1980-2002. Of those 1,465, 68.5% had one such episode, 1% had two, and 13.5% had three or more.

Age-adjusted incidence rates of dementia by frequency of severe hypoglycemic episodes were significantly higher among those with at least one episode, compared with those with no such episodes (566.8 vs. 327.6 per 10,000 person-years), with an attributable risk of 2.4% per year.

**Aiming for a very low glycemic target 'might not be beneficial and might even be harmful. We know high blood sugar isn't good, but … the message here is also that very low levels aren't good.'**

After adjustment for age, body mass index, race/ethnicity, education, sex, and diabetes duration, the hazard ratios for dementia, compared with patients who had no severe hypoglycemic episodes were 1.7 for those with at least one episode, 2.2 for two or more, and 2.6 for three or more episodes. Further adjustment for diabetes-related comorbidity, $HbA_{1c}$ level, diabetes treatment, and years of insulin use modestly attenuated the effect but it remained "statistically significant and clinically relevant" with hazard ratios of 1.3, 1.8, and 1.9, respectively, Dr. Whitmer and her associates said.

Trends were similar when only the incident dementia cases diagnosed between Jan. 1, 2005, and Jan. 15, 2007, were considered after adjustment for all the above-mentioned factors, with hazard ratios of 1.2 for at least one severe hypoglycemia episode, 1.7 for two or more episodes, and 2.1 for three or more episodes, compared with patients who had no such episodes. Another "backward lag model" analysis that examined only the impact of hypoglycemic events occurring from 1980 through 1985 also identified the same trend, with a hazard ratio of 1.3 for one or more episodes.

Other analyses, including adjustment for other variables indicative of diabetes severity, length of health plan membership, time since initial diabetes diagnosis, and medical utilization rate also yielded similar results, although there was some mild attenuation for patients with three or more episodes, the investigators said.

Possible mechanisms by which hypoglycemia might increase the risk of subsequent dementia in older individuals include neuronal death and/or increased platelet aggregation/fibrinogen formation. Cerebrovascular disease is another possibility, even though another analysis adjusting for acute stroke and transient cerebral ischemia in this study population did not fully account for the effect of hypoglycemia. Given evidence from animals, "cerebrovascular damage is likely one of the mechanisms," they noted.

Moreover, while hypoglycemia was not found to be associated with higher risk of subsequent impairment among the young adults with type 1 diabetes in the Diabetes Control and Complications Trial, "older individuals are thought to have less brain reserve or brain plasticity and therefore may be unable to recover from neurologic insult as well as younger individuals are able to," Dr. Whitmer and her associates said.

This study was funded by the National Institutes of Health. None of the investigators disclosed any conflicts of interest. ■