

# Obesity, Diabetes Trends Portend AD Wave

*Most effective method of treating cognitive impairment might be preventing insulin resistance.*

BY MICHELE G. SULLIVAN

VIENNA — If current trends in child and adolescent obesity continue, by 2040, one-third of the 81 million expected Alzheimer's cases worldwide may be a direct result of obesity-driven diabetes, according to researchers at the International Conference on Alzheimer's Disease who labeled the outlook as "dire."

"We need to identify the contributions to this increase in dementia and figure out how to decrease this burden," said Mary Haan, Ph.D., said at the meeting. "In the setting of diabetes and Alzheimer's, this means we need to think about intervening earlier in the process and treating across the life span. Our focus should be prevention, which is probably more effective when begun at younger ages."

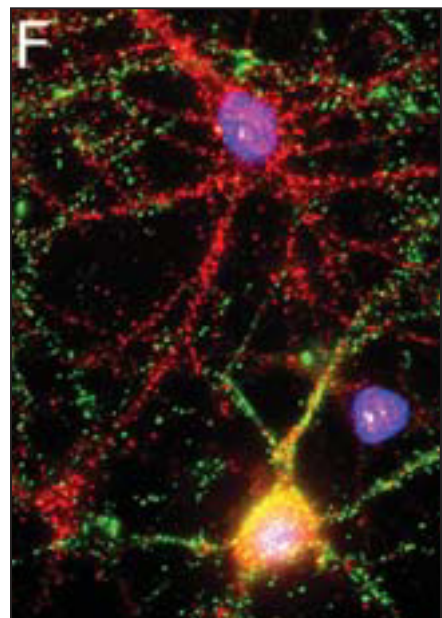
Dr. Haan is the primary investigator on the Sacramento Area Latino Study on Aging (SALSA), a prospective cohort study that has been ongoing since 1997. SALSA consists entirely of Mexican-Americans, whose high rates of type 2 diabetes, metabolic syndrome, and hypertension create an ideal population in which to study the impact of these disorders on cognition.

At the meeting, Dr. Haan of the University of California, San Francisco, presented 9 years of follow-up data on this group of 1,789 men and women (mean baseline age, 72 years). At study entrance, 33% of the group had type 2 diabetes and 40% had a body mass index of more than 25 kg/m<sup>2</sup>. More than half of the participants had metabolic syndrome.

Over 9 years, 158 incident cases of dementia or nondementia cognitive impairment developed. After controlling for age, gender, girth, diabetes treatment, fasting insulin, and C-reactive protein, Dr. Haan said the presence of diabetes at baseline more than doubled the risk of dementia or cognitive impairment.

ment. "This translates into a population attributable risk of 19%," she said. "Nineteen percent of all these dementia cases were the direct result of type 2 diabetes."

When carried forward in accordance with the projected increases in obesity, that 19% figure means that by 2040, 24 million cases of dementia could be di-



**The synapse deterioration seen in AD might be tied to the loss of insulin receptors (red) on dendrites of hippocampal neurons attacked by amyloid beta oligomers (green).**

rectly tied to type 2 diabetes, Dr. Haan said. Unfortunately, "there are no randomized controlled trials that support the notion that we should be treating [cognitive impairment] with an antidiabetic drug." Instead, the most effective method is probably to prevent obesity and insulin resistance.

Suzanne Craft, Ph.D., agreed. "The concern is this current epidemic of diabetes associated with insulin resistance, in conjunction with a rapidly aging population, foreshadows an epidemic of Alzheimer's."

And while it makes sense to investigate the impact that diabetes treatment might have on cognition, an incredibly effective intervention already exists.

"Exercise is the most potent insulin-sensitizing agent we have," said Dr. Craft, a geriatrician and Alzheimer's researcher at the Veterans Administration Puget Sound Health Care System, Seattle. "A single bout of aerobic exercise improves insulin sensitivity for 24 hours. It's much more potent than any medication. Caloric restriction also lowers hyperinsulinemia and improves insulin sensitivity."

A large body of work now suggests that insulin resistance increases the risk of Alzheimer's by multiple mechanisms, Dr. Craft said. Far from being active only in the periphery, insulin readily crosses the blood-brain barrier and binds to receptors located throughout the brain—especially in areas of strategic importance in cognition: the hippocampus, entorhinal cortex, and frontal cortex. Once in the brain, insulin interacts with amyloid beta in several ways, increasing its intracellular clearance through insulin degrading enzyme and apparently even protecting neurons from the protein's toxic effects.

"This has been known for some time, but recent research has shown that amyloid beta may have its own independent effects on insulin signaling," Dr. Craft said. A series of experiments by William L. Klein, Ph.D., concluded that soluble oligomers of amyloid beta can remove insulin receptors from the dendritic plasma membranes of hippocampal neurons. However, Dr. Craft said, "If insulin were administered before the oligomeric Aβeta, the dendritic spines were protected."

The study concluded that insulin receptor signaling downregulated the oligomeric binding sites. Adding rosiglitazone potentiated this effect, suggesting that insulin-sensitizing agents may have some role in cognitive protection (Proc. Natl. Acad. Sci. U.S.A. 2009;106:1971-6).

"Insulin appears to mitigate many of

the negative effects of amyloid and regulates its clearance, while beta amyloid appears to reduce insulin signaling. So high levels of insulin in the brain can induce a brain insulin-resistance by removing the insulin receptors from the nerve cell membranes," Dr. Craft said.

She recently investigated insulin's effect on memory in a group of 33 patients with Alzheimer's or mild cognitive impairment and 59 elderly controls. The patients received placebo or five escalating doses of intranasal insulin. Cognition was tested 15 minutes after each treatment. "We saw a 50% improvement in memory compared with baseline with the highest dose," Dr. Craft said (J. Alz. Dis. 2008;13:323-31).

In insulin resistance, there is a downregulation of the phosphoinositide-3 (PI3) kinase pathway, which mediates vascular relaxation. But the mitogen-activated protein (MAP) kinase pathway, which mediates vasoconstriction, is driven by high levels of insulin and thus, does not downregulate with insulin resistance. "You get a reduction in vasodilation and hyperactivation of vasoconstriction," Dr. Craft said.

She saw this in a recent study of 196 brains (71 with dementia). The brains were divided into four groups: normal; diabetic without dementia; diabetic with dementia; and dementia without diabetes (Arch. Neuro. 2009;66:315-22).

"We saw a surprising pattern when we looked at plaques and tangles: the brains of the patients with dementia but no diabetes had a high load, as anticipated, but the brains of diabetic patients with dementia had a plaque load that was similar to the normal controls," she said.

The patients with dementia and diabetes did, however, show high levels of microvascular lesions, which were absent in the other groups.

"The volume of the lesions is small, so they are almost certainly not directly responsible for the cognitive impairment, but this finding may point to some broader based vascular dysfunction," Dr. Craft said. ■

## Ginkgo's Ability to Boost Cognition Comes Up Short—Again

BY MARKETTE SMITH

**G**inkgo biloba shows no notable effect in reducing the incidence of dementia caused by Alzheimer's disease or dementia overall in older adults when compared with placebo, results of a recent study of more than 3,000 older adults show.

The latest findings are consistent with smaller trials, Beth E. Snitz, Ph.D., and her colleagues reported (JAMA 2009;302:2663-70).

In the current study, adults aged 72-96 years were monitored at six medical centers in the United States between 2000 and 2008 in the largest completed randomized, double-blind, placebo-controlled dementia prevention trial to date, according to Dr. Snitz, of the department of neurology at the University of Pittsburgh, and her colleagues. A total of 60% of subjects successfully completed the study; 54% were men.

Of the total, 1,545 participants were randomized to

receive a 120-mg dose of ginkgo biloba extract and 1,524 to receive placebo twice a day, Dr. Snitz noted. Follow-up included neuropsychological testing every 6 months until 2004 and once a year thereafter. The median follow-up was 6.1 years.

The placebo group performed better than did the ginkgo biloba group on 3 of 12 neuropsychological tests administered at baseline. Scores on other tests did not differ by treatment group. The ginkgo biloba and placebo groups did not differ on rates of cognitive change for the global cognition score or cognitive domains tested (memory, attention, visuospatial abilities, language, and executive functions).

In year 6 of the study, a secondary analysis was taken and results were consistent with the primary analysis; rates of cognitive change for the global score and all cognitive domains did not differ by treatment group, the investigators noted. In participants with early dementia or symptoms of cognitive impairment, results also indicat-

ed that 3 to 4 years of ginkgo biloba treatment had no significant effect on cognitive decline 2 to 3 years after use.

The clinical meaning of cognitive decline in this study was defined by a 4-point change in the Alzheimer Disease Scale.

"We [found] no evidence that *G. biloba* slows the rate of cognitive decline in older adults," wrote the investigators. "These findings are consistent with previous smaller studies examining prevention of decline and facilitation of cognitive performance and with the 2009 Cochrane review of *G. biloba* for dementia and cognitive impairment."

Funding for the study was provided in part through a grant from the National Center for Complementary and Alternative Medicine, a division of the National Institutes of Health. Ginkgo biloba extract tablets and placebo tablets were donated by Schwabe Pharmaceuticals.

Dr. Snitz and colleagues reported no relevant conflicts of interest. ■