**Obesity, Diabetes Trends Portend AD Wave**

**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/m². 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. “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 attributed to obesity, Dr. Haan said. The presence of diabetes at baseline more than doubled the risk of dementia or nondementia cognitive impairment. “Exercise is the most potent insulin-sensitizing agent we have,” 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 insulin receptors 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 Abeta, the dendritic spines were protected.”

The study concluded that insulin resistance signaling downstream to 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 downstream inhibition of the phosphoinositide-3 (PI3) kinase pathway, which mediates vascular relaxation. But the mitogen-activated protein (MAP) kinase pathway, which mediates vasodistraction, is driven by high levels of insulin and thus, does not downregulate with insulin resistance. “We don’t see downregulation 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. Neurol. 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.

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**Ginkgo’s Ability to Boost Cognition Comes Up Short Again**

**BY MARKETTE SMITH**

Ginkgo 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).

The placebo group performed better than did the ginkgo biloba group on 3 of 12 neuropsychological tests administered at baseline. Scores on these 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 that used data from 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 indicated 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 investi- gators. “The results were 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, part 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.