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Diabetes, Insulin Resistance Linked to Alzheimer's

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MedPage Today Action Points

- Explain to interested patients that a Japanese autopsy study found an association between hyperglycemia and insulin resistance documented during the decade before death and neuritic plaques -- one pathologic finding of Alzheimer's disease -- at autopsy.
- Note that the study was small and there was no association between the diabetes-related factors and neurofibrillary tangles connected to amyloid deposits, a different pathologic finding in Alzheimer's.

Review

Insulin resistance and type 2 diabetes may contribute to the development of one type of brain plaque linked to Alzheimer's disease, according to an autopsy study.

An analysis of autopsy samples from 135 Japanese men and women found that high insulin and glucose levels appeared to accelerate the formation of neuritic plaques, especially among those carrying a high-risk gene for Alzheimer's, Kensuke Sasaki, MD, PhD, of Kyushu University in Fukuoka City, Japan, and colleagues, reported.

The association of neuritic plaques with higher levels of two-hour post-load plasma glucose, fasting insulin, and insulin resistance measured in the decade before death was found to be independent of other risk factors like age, blood pressure, smoking, and cerebrovascular disease, Sasaki and co-authors wrote in the Aug. 25 issue of *Neurology*.

Thus, "adequate control of diabetes might contribute to a strategy for the prevention of Alzheimer's disease," they concluded.

Although these findings strengthen evidence for a causal link with dementia, an accompanying editorial by José A. Luchsinger, MD, MPH, of Columbia University Medical Center and School of Public Health in New York City, cautioned that alternative explanations must be considered.

For example, Luchsinger noted, the relatively small sample size selected from a much larger pool of participants who did not have an autopsy may have led to selection bias or to chance findings.

Reverse causality was also a possibility since brain pathology and metabolic changes may precede dementia diagnosis by decades and diabetes and insulin resistance could result from or correlate with Alzheimer's, he added.

On the assumption that the association may be causal, though, several randomized trials are already testing insulin sensitizers in older adults or those with mild cognitive impairment to see if the strategy has an effect on cognition.

"This is urgent considering that over half the U.S. population in the age group most at risk for cognitive impairment has prediabetes or type 2 diabetes, preceded or accompanied by insulin resistance and hyperinsulinemia," Luchsinger concluded in the editorial.

The researchers analyzed autopsy results from 74 men and 64 women (average age 67) who died between 1998 and 2003 after participating in the long-term prospective Hisayama Study, which looked at cerebro-cardiovascular diseases among almost 3,400 residents of the Japanese town. During this period 290 Hisayama residents died and 214 were autopsied (73.8%).

A total of 2,520 participants had received oral glucose tolerance tests in 1988 and were free of signs of dementia at that time. During the ensuing decades, 15.6% developed Alzheimer's-type dementia.

However, among the 135 participants autopsied, 65% actually had neuritic plaques characteristic of Alzheimer's disease.

Presence of these plaques was associated with significantly higher levels of the following after adjustment for age, sex, and a full set of potential confounders:

- Two-hour post-load plasma glucose in a 75-g oral glucose tolerance test (odds ratio 1.71, $P=0.03$)
- Fasting insulin (OR 2.03, $P=0.02$)
- Insulin resistance measured by the homeostasis model of assessment (HOMA-IR, OR 2.11, $P=0.01$)

These endocrine factors also appeared to combine with genetic risk to accelerate formation of neuritic plaques.

Those with low glucose levels on the glucose tolerance test who didn't carry the *apolipoprotein E-4* gene (*APOE-4*) allele associated with Alzheimer's disease were least likely to show neuritic plaques in their brain on autopsy whereas hyperglycemia alone was associated with 1.5-fold risk and the *APOE* carriers had 19.7-fold risk.

The greatest likelihood of neuritic plaques was seen in those with both hyperglycemia and the *APOE* allele (38.0-fold compared with neither).

The pattern was similar for fasting insulin and insulin resistance, although the interactions with the *APOE* genotype weren't statistically significant.

Neurofibrillary tangles -- another type of brain pathology seen with Alzheimer's disease

considered to be due to beta-amyloid plaque deposition -- correlated neither with any insulin or glucose measures nor with the presence of neuritic plaques.

"The diabetes-related factors may act upstream of the cascade, and might trigger the Alzheimer's disease pathogenesis," Sasaki's group suggested in the paper.

The authors cited several limitations to their study: First, the crude, semiquantitative evaluations of neuritic plaques could have affected the statistical analyses, and "the medical history of diabetes, such as disease duration, glucose control, and complications, were not considered in this study," they wrote.

The study was supported by a grants from the Ministry of Health, Labour and Welfare of Japan and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Matsuzaki reported having no conflicts of interest to disclose.

Co-authors reported having received research support from the Ministry of Health, Labor and Welfare of Japan; having served on scientific advisory boards for Eli Lilly, GlaxoSmithKline, Pfizer, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Astellas Pharma, Asahi Kasei, Shionogi, and Otsuka Pharmaceutical; having served on the editorial boards of multiple journals; having received speaker honoraria from Eli Lilly, GlaxoSmithKline, Pfizer, Asahi Kasei, Janssen, Tsumura, Ajinomoto, Mitsubishi Tanabe Pharma, Meiji Techno, Kyowa Hakko Kirin Pharma, Dainippon Sumitomo Pharma, Organon International (Schering-Plough), Otsuka Pharmaceutical, and Astellas Pharma; and having received research support from Eli Lilly, GlaxoSmithKline, Pfizer, Asahi Kasei, Janssen, Tsumura, Ajinomoto, Mitsubishi Tanabe Pharma, Meiji Techno, Kyowa Hakko Kirin Pharma, Dainippon Sumitomo Pharma, Organon International (Schering-Plough), Otsuka Pharmaceutical, and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Luchsinger JA "Insulin resistance, type 2 diabetes, and AD: Cerebrovascular disease or neurodegeneration?" *Neurology* 2010; 75: 758–759.

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