

Transcript Details

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Linking Obesity to Alzheimer's: The Lipid Signals Driving Neurodegeneration

Announcer:

You're listening to *Clinician's Roundtable* on ReachMD. On this episode, Dr. Stephen Wong will discuss new research on the link between obesity and Alzheimer's disease. Dr. Wong is the John S. Dunn Presidential Distinguished Chair in Biomedical Engineering at Houston Methodist Hospital and Associate Director at Houston Methodist Cancer Center. He's also a Professor of Radiology, Neurosciences, Pathology, and Laboratory Medicine at Weill Cornell Medicine. Let's hear from him now.

Dr. Wong:

Alzheimer's and obesity are two of the fastest-growing health problems—not just in the U.S., by the way. It's really the whole world. Right now, about seven million Americans are living with Alzheimer's, and that number is expected to almost double by 2050.

At the same time, more than 42 percent of adults are obese. And these two diseases might sound like very different conditions, but biologically, they share chronic inflammation, metabolic imbalance, and disruptions in how the body processes lipids.

Now, we should know that the brain is a very lipid-rich organ—very fatty—and healthy lipid metabolism is very critical for neurons and glial cell to function properly. In obesity, fat isn't sitting there storing energy. It becomes an active organ to release a whole bunch of molecules in the bloodstream. And among all these signals, what caught our attention was the extracellular vesicles. And you can think of them as a tiny bubble-like package that fat cells release that are filled with all this bioactive cargo, like lipids, proteins, and RNAs.

The fascinating thing is that, unlike most hormones or other small molecule antibodies, EV—extracellular vesicles—can actually cross the blood-brain barrier and deliver their cargo directly to the brain cells. And in obesity, the amount and composition of these vesicles change dramatically, and we believe these altered vesicles may be sending a harmful metabolic message to the brain—one that will trigger inflammation, oxidation, stress, or amyloid buildup. They're all key hallmarks of Alzheimer's.

We tried to build a bridge between what's happening in people with obesity and what's happening in Alzheimer's biology at the molecular level. If obesity changes the lipid signals the body sends out and those signals can reach the brain through extracellular vesicles, then what exactly do those vesicles carry, and how might that cargo affect the key Alzheimer's process—the amyloid aggregation?

First, we focused on collecting and categorizing these messengers. We isolated very pure EVs from adipose tissues. And then we double-checked their quality and made sure their size, shape, and quality control were all very good. And then to be sure, we studied real true vesicles—not any contaminants because they're so tiny. The second part was we characterized what those vesicles were carrying. And third, finally, we tested how these individual lipid species affect amyloid beta aggregation—a central process of Alzheimer's.

Then, we looked at the results. Different lipid species changed amyloid aggregation in very unique patterns depending on the concentration. We also found not all amyloid behaves the same. There are two major forms—we call it amyloid 40 and amyloid 42—that respond differently with the same lipid species. What that means is these peptides interact with lipids in very distinct ways, possibly shifting the balance between more or less toxic forms, and that's important because those structure changes can drive very different outcomes of brain health.

We treat Alzheimer's disease as one big thing. In reality, it's not. And besides subtyping of Alzheimer's, we also should think about individualized Alzheimer's because we're all different. Lipidomic profiling can help tailor care. That's one thing. And second is, at the

same time, we can use it as a biomarker—not just for detection, but for monitoring when you're treating the patient.

Announcer:

That was Dr. Stephen Wong discussing a relationship between obesity and Alzheimer's disease. To access this and other episodes in our series, visit *Clinician's Roundtable* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!