

Type 2 Diabetes Likened to Alzheimer's Disease

BY TIMOTHY F. KIRN
Sacramento Bureau

SEATTLE — Type 2 diabetes is more than just the loss of insulin sensitivity. It also is clearly related to a loss of β -cells and islet function, probably mediated to some extent by amyloid deposits, Dr. Stephen E. Kahn said at the annual meeting of the American Association of Clinical Endocrinologists.

The disease process of type 2 diabetes "appears to be very similar in many ways to what happens in Alzheimer's disease," said Dr. Kahn, a professor of internal medicine at the University of Washington, Seattle.

Studies by his group and others have clearly shown that persons with type 2 diabetes have attenuated insulin secretion in response to glucose and that the beginning of this loss of β cells, and β -cell function, precedes the development of diabetes in many cases, he said.

This explains why the trial known as ADOPT (A Diabetes Outcome Progression Trial)

The experiments showed that there was a clear correlation between the amount of amyloid deposited and the number of β -cell deaths.

showed that rosiglitazone treatment was better than metformin at curtailing progression of type 2 diabetes, and metformin was better than glyburide, said Dr. Kahn, who is also an associate chief of staff at the Veterans Affairs Puget Sound Health Care System in Washington.

The study showed that rosiglitazone treatment resulted in a 62% reduction in risk of progression from monotherapy of type 2 diabetes to add-on therapy relative to glyburide, and a 32% risk reduction relative to metformin (*N. Engl. J. Med.* 2006;355:2427-43).

The reason was that glyburide increased insulin secretion but did not change insulin sensitivity, so over time, the β cells could not keep up, Dr. Kahn said. Rosiglitazone and metformin, on the other hand, increased insulin sensitivity, lessening the demand on the β cells and preserving their function.

Although there are a number of causes that may be leading to β -cell loss, Dr. Kahn said his recent research has demonstrated that part of it is caused by the deposition of amyloid.

To conduct those experiments, Dr. Kahn and his colleagues had to develop a transgenic mouse that gets amyloid deposits in its islets, something that does not happen normally in the mouse but does happen in humans with type 2 diabetes.

With these mice, Dr. Kahn's group has shown that feeding the animals a high-fat diet resulted in more islets with amyloid deposits, a greater portion of each islet given over to amyloid at the expense of β cells, and a decline insulin secretion (*Diabetes* 2003;52:372-9).

Next, his group treated the mice with rosiglitazone and metformin while feeding them the high-fat diet, and showed that the treatment prevented amyloid deposition. This occurred presumably because the β cells were not working as hard when the mice were on one of those drugs, and deposition is related to how hard the cells are functioning (*Diabetes* 2005;54:2235-44).

"It's clearly very provocative and suggests that this may be one mechanism by which these drugs provide better durabil-

ity than sulfonylureas, which we would predict would increase secretion and result in more amyloid production on a high-fat diet," he said.

Most recently, his group has looked at why islet transplants fail using this model, because it has been clear for some time that failure is not because of the autoimmune response attacking β cells only. To look at this, they transplanted two groups of mice: one group with transgenic islets that could produce amyloid deposits like

a human and one group with nontransgenic islets.

The experiments showed that in the 11 of 12 mice with amyloid potential, the amyloid deposits actually occurred and that there was a clear correlation between the amount of amyloid deposited and the number of β -cell deaths.

They also found that amyloid appeared to prevent new β -cell replication, Dr. Kahn said. "This is the mechanism that might also be going on in type 2 diabetes." ■

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