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## Diabetes in the Elderly Linked to Fewer Cellular "Power Plants"

Elderly people may develop insulin resistance—one of the major risk factors for diabetes—because “power plants” in their muscle cells decline or fail with age, according to Howard Hughes Medical Institute researchers at Yale University School of Medicine.

In studies of young and elderly people, the researchers found that older people had lower levels of metabolic activity in their mitochondria, the “factories” that provide power to cells. The findings suggest that reduced mitochondrial activity underlies insulin resistance, which is a major contributor to type 2 diabetes in the elderly.

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**— Gerald I. Shulman**

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In another recent study the researchers also found that physical activity can enhance the number of mitochondria in muscle by activation of a key enzyme called AMP kinase. “This is yet another reason for seniors to maintain an active lifestyle,” said the study's senior author, Gerald Shulman of the Howard Hughes Medical Institute at Yale. Shulman and his colleagues reported their findings in the May 16, 2003, issue of the journal *Science*.

According to Shulman, pinpointing the cause of type 2 diabetes in the elderly would help solve a major health problem. “Approximately one in four individuals over the age of 60 has type 2 diabetes, which is a remarkable statistic,” said Shulman. “And, if you add impaired glucose tolerance, you're talking about forty percent of the population.”

The estimated economic burden of diabetes in United States is about \$100 billion per year, a substantial proportion of which is due to diabetes in the elderly, said the researchers.

At the biochemical level, the hormone insulin promotes the transfer of glucose in the blood into cells for energy production and storage. Mitochondria within the cells convert glucose and fatty acids into energy via

oxidation.

According to Shulman, previous studies in his laboratory had shown that insulin resistance in muscle and liver tissue can result from accumulation of fat and fatty acid metabolites.

“We hypothesized that there were two routes to this type of fat accumulation,” said Shulman. “One is that the fat cells might release more fatty acids to be delivered to muscles and/or defects in mitochondrial oxidation might then lead to the accumulation of these fatty acids.”

To trace the cause of insulin resistance in the elderly, the researchers compared glucose and fatty acid metabolism in matched groups of older and younger people. “One possibility is that as people age, they are less active and put on weight, and those factors are contributing to insulin resistance and diabetes,” he said. “So a key aspect of this study is that our older and younger samples of people were matched for fat mass, lean body mass and physical activity habits.” The sample groups consisted of 16 elderly volunteers, aged 61 to 84 years, and 13 younger volunteers, aged 18 to 39.

In initial metabolic tests of the effectiveness of insulin in the two groups, Shulman and his colleagues found significantly higher insulin resistance in the elderly subjects. They traced the insulin resistance to muscle tissue, using a non-radioactive “heavy” tracer isotope and techniques to measure insulin resistance.

The researchers next turned to nuclear magnetic resonance spectroscopy (NMR), to zero in on muscle cells to determine whether they were accumulating fat. In NMR spectroscopy, harmless magnetic fields and radio frequency pulses are used to detect and quantify signals characteristic of specific molecules. The NMR studies revealed that the elderly subjects showed much higher fat accumulation in their muscle cells.

“This finding is important because studies in our lab and others have shown that the amount of lipid inside the muscle cell is a very good predictor of insulin resistance,” said Shulman.

Studies of the fat tissue in the elderly subjects showed that the fat cells were not releasing the extra fat that was accumulating in muscle. Thus, reasoned the researchers, the fatty molecules in the muscle cells might be accumulating due to defects in the cells' fat-burning mitochondria.

Using NMR to follow chemicals labeled with non-radioactive tracer isotopes, the researchers could specifically measure the metabolism of fat in functioning mitochondria within the subjects' muscle cells. Those studies revealed that, indeed, mitochondrial activity was reduced by about 40 percent in the cells of the elderly subjects, compared with the young.

Shulman theorizes that if the same mitochondrial defects occur in the insulin-producing cells of the pancreas, the progression from insulin resistance to diabetes will be complete.

Shulman said that before researchers can develop new clinical treatments to enhance mitochondrial function and thus help prevent diabetes, they must understand a great deal more about mitochondria. More basic research is needed to understand whether the number or individual activity of mitochondria are reduced in the elderly, as well as the role of mutations or other factors in such age-related reductions, he said.

“However, an encouraging note in this study is that—since we've shown that exercise leads to more mitochondria by activation of AMP kinase—by staying active, the elderly might well be able to maintain mitochondrial content and head off such health problems,” said Shulman. To test that possibility, the researchers also plan studies to compare mitochondrial activity in active and sedentary elderly people.