Drug prevents Type 2 diabetes in majority of high-risk individuals

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A pill taken once a day in the morning prevented type 2 diabetes in more than 70 percent of individuals whose obesity, ethnicity and other markers put them at highest risk for the disease, U.S. scientists reported today.

The team also noted a 31 percent decrease in the rate of thickening of the carotid artery, the major vessel that supplies blood to the brain. The study, which enrolled 602 participants through The University of Texas Health Science Center San Antonio and seven collaborating centers, is described in the New England Journal of Medicine and has direct implications for the care of 40 million Americans who are pre-diabetic.

"It's a blockbuster study," said senior author Ralph DeFronzo, M.D., professor in the School of Medicine and chief of the diabetes division at the UT Health Science Center San Antonio. "The 72 percent reduction is the largest decrease in the conversion rate of pre-diabetes to diabetes that has ever been demonstrated by any intervention, be it diet, exercise or medication."

Multiple-year follow-up

Dr. DeFronzo led the trial of pioglitazone, which is marketed as Actos by Takeda Pharmaceutical Co. Ltd. The Japanese company provided an independent investigator grant to Dr. DeFronzo to conduct the ACT Now study. Some patients were followed for as long as four years; the

average follow-up was 2.4 years.

Pioglitazone is widely used as an insulin sensitizer in patients with type 2 diabetes. In the ACT Now study, participants were chosen because of their high risk for diabetes, including obesity, family history and impaired glucose tolerance as demonstrated by a glucose test.

"The drug shows outstanding results," said Robert R. Henry, M.D., president, medicine and science, of the American Diabetes Association. "It is the most efficacious method we have studied to date to delay or prevent the onset of type 2 diabetes." A study co-investigator, Dr. Henry is professor of medicine at the University of California, San Diego, and chief of the section of endocrinology and diabetes at the VA San Diego Healthcare System.

Blood vessel damage prevented

Robert Chilton, D.O., FACC, a UT Health Science Center San Antonio cardiologist who was not involved with the study, said the slowing of carotid artery thickness indicated that the participants' glucose was well controlled, preventing blood vessel damage that leads to heart attacks, strokes and peripheral vascular disease.

Individuals who have diabetes have the same high risk of having a first heart attack as do non-diabetic people who already had a heart attack, he noted.

"The drug was able to postpone conversion to diabetes in 72 percent of people," Dr. Chilton said. "The only thing that could potentially beat that is the free pill no one seems to be able to take – diet and exercise."

Insulin resistance

Type 2 diabetes involves abnormalities with insulin, a hormone secreted by beta cells in the pancreas. Insulin helps the body store and use sugar from food, but in type 2 diabetes the body is insulin resistant, that is, it inefficiently responds to the hormone. With time the beta cells in diabetic patients start to die, resulting in less insulin to handle the demands. Levels of the hormone become progressively lower and sugar levels are increased progressively, damaging blood vessels and organs.

Dr. Henry said the ACT Now study highlights the importance of insulin resistance in the development of type 2 diabetes and how, by treating this resistance, the beta cell secretion of insulin is preserved for a longer period of time.

Pioglitazone was well tolerated by participants, with weight gain and fluid retention observed at the dose used in the study. Dr. DeFronzo said those side effects can be mitigated by using a lower dose that works equally well. Pioglitazone stimulates appetite while at the same time shifting fat around in the body, taking it out of muscle, the liver and beta cells and putting it in subcutaneous fat depots under the skin where it is inert and not harmful, he said.

"No drug is perfect," Dr. DeFronzo said. "This particular medication does two things – improves insulin resistance and improves beta cell function, which are the two core defects of diabetes."

More information: Pioglitazone for Prevention of Diabetes in Impaired Glucose Tolerance, Ralph A. DeFronzo, et al., *New England Journal of Medicine*.

Provided by University of Texas Health Science Center at San Antonio