Early treatment with basal insulin glargine in people with type 2 diabetes: Lessons from ORIGIN and other cardiovascular trials

The inability to control blood glucose levels can result in many negative health outcomes including eye, kidney, cardiovascular (heart) and foot disease, and early death. Persons with type 2 diabetes are 2 to 4 times more likely to develop heart disease than those without diabetes. The higher-than-normal blood glucose levels seen in these people are the result of inadequate insulin secretion together with an inability of the body to respond to insulin correctly. If left uncorrected, the high blood glucose, combined with high fat levels, can lead to the death of the cells in the pancreas (beta cells) that produce, store and release insulin which the body needs to keep blood glucose levels within the normal range throughout the day and nighttime.

Many studies have shown that high glucose concentrations over time impair the function of the beta cells and that lowering glucose can reverse this glucotoxic effect and restore beta cell function. Insulin injections given early on as part of the treatment for type 2 diabetes can by reducing the blood glucose to near normal levels greatly improve beta cell function. In one study, the early introduction of insulin for a short period of time (2 to 4 weeks) led to near-normal glucose levels in about half the subjects in the absence of any other treatment for a period of one or two years. While metformin is considered the first line of treatment in patients with type 2 diabetes, only insulin has been shown to provide consistent lowering of blood glucose to normal. Introducing insulin early in support of metformin has been shown to be an effective combination in large scale studies with minimal effect on weight gain and risk of hypoglycemia.

Heart disease is a major cause of disability and death in people with type 2 diabetes. In a review of very large clinical trials, those with diabetes over a long period of time had fewer heart attacks with intensive blood glucose control but no other heart-related benefits, even a higher mortality rate was seen with intensive treatment. Although intensive glucose control shows benefits for the eyes and kidneys after 5-10 years of follow-up, significant improvements in the prevention of heart disease have only been shown after a much longer follow-up period.

The ORIGIN, or Outcome Reduction with an Initial Glargine Intervention trial, looked at whether the long-acting insulin, insulin glargine, had an unwanted effect on heart-related outcomes in 12,537 persons with pre-diabetes or type 2 diabetes and a history of heart-related problems after 6.2 years of follow-up. A very conservative dose titration algorithm was used because insulin glargine was started at an early stage of glucose intolerance. Overall, the study found that insulin glargine was safe and did not increase the risk for heart-related complications or cancer. Severe hypoglycemia was however higher with insulin, as expected, and there was moderate weight gain with the use of insulin glargine. In participants with pre-diabetes, the worsening of their glucose control was slowed and these benefits remained 3 years after the study ended. Many believe that a longer follow-up time in the ORIGIN trial may help to reveal the true benefit of early insulin in this population with

type 2 diabetes at a high risk of cardiovascular disease.

Therefore, the use of insulin early has been shown to improve blood glucose levels, reduce the adverse effects of high blood glucose, and to restore/maintain the function of the pancreatic beta cells. The results of ORIGIN support the safe use and potential long-term benefit of the early introduction of insulin therapy, in the form of the basal insulin glargine, in persons with type 2 diabetes.

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