Heredity Strongly Influences Insulin Clearance

BY BETSY BATES

Insulin clearance is a highly heritable trait that has now been tracked to specific regions of two chromosomes, a finding that may have important implications for risk assessment in diabetes, polycystic ovary syndrome, and metabolic syndrome.

Although it has been "virtually neglected" in studies of insulin metabolism, insulin clearance may strongly influence an individual's risk of diabetes and response to the diabetic state, Dr. Mark Goodarzi reported at the Western regional meeting of the American Federation for Medical Research in Carmel, Calif.

In previous work, Dr. Goodarzi and his associates had raised the possibility that the metabolic clearance rate of insulin was largely an inherited trait, because of patterns seen in a cohort of 403 Mexican American subjects (Diabetes 2005; 54:1222-7).

The current study by these investigators of a second cohort of 536 individuals from 162 Hispanic families found that insulin clearance was indeed a highly heritable trait, with an age-, sex- and body mass index–adjusted heritability rate of 70.5%.

A genomewide linkage scan applied to samples from the same population identified candidate regions on chromosomes 15 and 20 that may harbor genes that influence insulin clearance, Dr. Goodarzi said in an interview.

Insulin clearance is a relatively unknown player in the sequence of events leading to diabetes.

A recent Medline search revealed more than 35,000 references to insulin resistance and more than 16,000 references to insulin secretion, but just 424 references to insulin clearance.

Although the significance of insulin clearance is underappreciated, it may prove to have an important role as a marker of risk or a target for intervention not only for diabetes, but also for other disorders characterized by hyperinsulinemia, such as polycystic ovary syndrome.

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DR. GOODARZI

"It appears that a reduction in insulin clearance may be a compensatory response to the insulin resistant state, acting in concert with increased insulin secretion to increase insulin levels," Dr. Goodarzi explained.

"If insulin levels increase sufficiently, the insulin resistance may be overcome and blood sugars will be maintained in the normal range. However, if there is a failure to adequately increase insulin levels in the face of insulin resistance—either by failing to increase insulin secretion, or, theoretically, failing to reduce insulin clearance—then diabetes will develop," said Dr. Goodarzi, associate director of the division of endocrinology at Cedars-Sinai Medical Center, Los Angeles.

To test for heritability, subjects were drawn from the offspring generation within MA-HTN, a Mexican American Hypertension study of 939 subjects from 162 families.

Mexican Americans were chosen to participate in the study because of their high prevalence of insulin resistance and high age-specific prevalence of metabolic syndrome.

To date, genetic studies of diabetes, insulin resistance, insulin secretion, and insulin clearance "have not yet translated to clinically useful tools," Dr. Goodarzi said.

However, he predicted that the time is not far off—perhaps 5-10 years—when such a link can be made, perhaps by influencing clinical outcomes by implementing interventions once individuals at risk are identified through genetic testing.

Dr. Goodarzi and his associates did not disclose any potential conflicts of interest regarding their research. ■

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