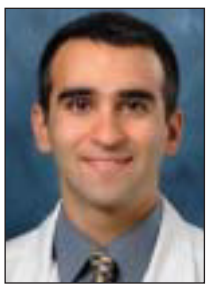
Heredity Strongly Influences Insulin Clearance

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 the metabolic syndrome.

Although it has been "virtually neglected" in studies of insulin metabolism, insulin clearance may strongly impact 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 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).

Their current study 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 genome-wide linkage scan applied to samples from the same population identified candidate regions on chromosomes 15 and 20 that may harbor genes influencing insulin clearance, Dr. Goodarzi 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, more than 16,000 references to insulin secretion, but just 424 references to insulin clearance.

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

To date, genetic studies of diabetes and insulin resistance have not yet translated to useful tools.

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 for the study because of their high prevalence of insulin resistance and high age-specific prevalence of the metabolic syndrome.

Euglycemic clamps were used to measure insulin sensitivity and clearance, keeping the insulin infusion rate steady for all subjects and obtaining a direct measure of insulin clearance via steady state plasma insulin (SSPI) levels achieved during the clamp study.

Once it was determined that more than 70% of the variation in insulin clearance was due to genetic factors, a genome-wide linkage scan utilizing 388 microsatellites resulted in the discovery of SSPI linkages on chromosomes 15 and 20.

Dr. Joseph M. Vinetz, AFMR western section president, said in a telephone interview that Dr. Goodarzi's study had the potential of "optimizing care in the exploding epidemic of type 2 diabetes," with "huge ramifications for early prevention throughout society."

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

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 conflicts of interest regarding their research. ■

Use of Glitazone Associated With Diabetic Macular Edema

BY MARK S. LESNEY

Glitazone use was associated with an increased risk of diabetic macular edema even after accounting for confounding factors, according to the results of a large, prospective cohort study.

Insulin use and meglitinide use also resulted in statistically significant increases in the risk of diabetic macular edema (ME), the analysis found.

Glitazones (thiazolidinediones) are used to reduce insulin resistance in patients with type 2 diabetes. One of the most commonly used drugs in this class is pioglitazone (Actos). Some studies have found pedal edema in 3%-5% of glitazone users, and others have suggested an association between glitazones and ME.

More than 170,000 persons listed in the Diabetes Case Identification Database were included in a study conducted by Kaiser Permanente Southern California. Glitazone use was based on records in the pharmacy database, and the main outcome measure was the development of ME, according to Dr. Donald S. Fong and Richard Contreras from the Southern California Permanente Medical Group offices in Baldwin Park and Pasadena.

For the years 2002-2006, 143,257 patients with diabetes had a drug benefit. Of these, 59,013 patients had at least one eye exam in 2006, and in that year, 996 new cases of ME were identified. In the total population, 17,078 patients were treated with glitazones, 98% of whom were treated with pioglitazone.

In a direct comparison, all individuals who were being treated with glitazones showed a higher risk of developing ME in 2006 (odds ratio, 2.6; 95% confidence interval, 2.4-3.0). After excluding patients who did not have a drug benefit or an eye exam and who had an hemoglobin A_{1c} level less than 7.0, the investigators found that glitazone use was still associated with an increased risk of ME (OR, 1.6).

Individuals treated with glitazones showed a 2.6 odds ratio of developing macular edema.

DR. FONG

Insulin and meglitinide also appeared to increase the risk of diabetic ME. However, metformin and acarbose use was not associated with ME.

An interactive model that was used to explore the relationship between insulin and glitazone showed that although both drugs separately are associated with an increased risk of ME, the risk is less when individuals take both drugs (Am. J. Ophthalmol. 2009 [doi:10.1016/j.ajo.2008.10.016]).

The researchers reported that they had no financial support or financial conflicts of interest with regard to their paper. ■

Diabetes, Prediabetes Top 40% Among U.S. Adults

BY HEIDI SPLETE

More than 40% of American adults aged 20 years and older have hyperglycemic conditions, according to review of data from the 2005-2006 National Health and Nutrition Examination Survey.

In this study, Catherine Cowie, Ph.D., of the National Institutes of Health and her colleagues compared NHANES data for 1988-1994 with data for 2005-2006 (Diabetes Care 2009;32:287-94).

The crude prevalence of diabetes, including diagnosed and undiagnosed cases based on fasting plasma glucose or 2-hour glucose tests, was 13% in individuals aged 20 years and older. The total diabetes prevalence peaked at about 30% among all age groups older than 60 years, and the prevalence of diabetes was approximately the same in both men and women.

After the researchers controlled for age and sex, the total diabetes prevalence was 70% higher in non-Hispanic blacks and 80% higher in Mexican Americans, compared with non-Hispanic whites.

The total crude prevalence of prediabetes, including both diagnosed and undiagnosed cases based on impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) tests was 30%, and this prevalence was highest among individuals aged 75 years and older, where it reached 47%.

The prevalence of diabetes and prediabetes, both diagnosed and undiagnosed, was significantly higher in men, compared with women (48% vs. 34%) but most of this difference was because of the greater prevalence of prediabetes among men. And the prevalence of any hyperglycemic condition was significantly higher in non-Hispanic blacks, compared with whites (44% vs. 39%) and in Mexican Americans vs. non-Hispanic whites (52% vs. 39%).

When the researchers compared the 2005-2006 data with the data for 1988-1994, they found that the crude prevalence of diagnosed diabetes rose significantly, from 5% to 8%.

"The sheer magnitude of prevalence of hyperglycemic conditions found in 2005-2006 portends all the consequences of diabetes," the researchers wrote.

The results were limited by the use of a single plasma glucose reading for some cases of undiagnosed diabetes and prediabetes, the investigators reported.

But the findings illustrate the chronic problem of diabetes and prediabetes in the United States and support the need for lifestyle modification for individuals with diabetes or prediabetes, said the researchers, who had no financial conflicts to disclose. ■