Patients with mild hyperglycemia and genetic mutation have low prevalence of vascular complications

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Despite having mild hyperglycemia for approximately 50 years, patients with a mutation in the gene encoding the enzyme glucokinase had a low prevalence of clinically significant vascular complications, findings that provide insights into the risks associated with isolated mild hyperglycemia, according to a study in the January 15 issue of *JAMA*.

"In both type 1 and type 2 diabetes, hyperglycemia [abnormally high blood sugar] is associated with microvascular complications over time. Intensive treatment to lower blood glucose levels reduces the development of microvascular complications," according to background information in the article. Certain patients with glucokinase (GCK) mutations have mild fasting hyperglycemia from birth, resulting in an elevated glycated hemoglobin (HbA1c) level that mimics recommended levels for type 1 and type 2 diabetes.

Anna M. Steele, Ph.D., of the University of Exeter, United Kingdom, and colleagues assessed the prevalence and severity of microvascular and macrovascular complications in patients with GCK mutations to provide additional information about the relationship between current glycemic targets and diabetes-related complications. The study, conducted in the United Kingdom between August 2008 and December 2010, included 99 GCK mutation carriers (median [midpoint] age, 49 years), 91 nondiabetic, nonmutation carrier relatives (control) (median age, 52 years), and 83 individuals with young-onset type 2 diabetes (YT2D),

diagnosed at age 45 years or younger (median age, 55 years). Median HbA1c was 6.9 percent in patients with the GCK mutation, 5.8 percent in controls, and 7.8 percent in patients with YT2D.

The prevalence of clinically significant microvascular complications (such as retinopathy, nephropathy, and neuropathy) was low in patients with a GCK mutation (1 percent) and the control group (2 percent). In contrast, 36 percent of the YT2D group had evidence of clinically significant microvascular disease. Thirty percent of patients with GCK had retinopathy compared with 14 percent of controls and 63 percent of patients with YT2D.

Neither patients with GCK nor controls had proteinuria (the presence of excessive protein in the urine), and microalbuminuria (an increase in the urinary excretion of the protein albumin that cannot be detected by a conventional test) was rare, whereas 10 percent of YT2D patients had proteinuria and 21 percent had microalbuminuria. Neuropathy was rare in patients with GCK and controls but present in 29 percent of YT2D patients. Patients with GCK had a low prevalence of clinically significant macrovascular complications (4 percent; such as heart attack, ischemic heart disease, stroke) that was not significantly different from controls (11 percent), and lower in prevalence than patients with YT2D (30 percent).

The presence of ischemic heart disease was low in the GCK and control group, while higher in YT2D patients (16 percent). No patients in either the GCK or control groups had experienced a stroke compared with 4 of 83 patients (5 percent) in the YT2D group.

"Patients with a GCK mutation have a low prevalence of clinically significant microvascular and macrovascular complications despite their lifelong hyperglycemia. In these patients, an average of nearly 50 years of isolated hyperglycemia within current target ranges for diabetes

control has a negligible association with complication development," the authors conclude.

Jose C. Florez, M.D., Ph.D., of Massachusetts General Hospital, Boston, comments on the findings of this study in an accompanying editorial.

"… this study by Steele et al sheds light on the extent to which decades of isolated mild hyperglycemia promote diabetes complications, and with key caveats expressed here [within the editorial], this study supports current treatment goals and lays the groundwork for more extended follow-up of this unique population," Dr. Florez writes. "Overall, it is clear that despite the low frequency of glucokinase maturity-onset diabetes of the young, knowledge of its natural course has implications for the management of common forms of diabetes, and it illustrates how clinical insights gained from the study of monogenic [pertaining to one gene] syndromes can improve understanding of complex diseases."

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