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Cardiovascular diseases and diabetes: causes and cures

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Abstract

The relationship between type 2 diabetes and an increased cardiovascular risk involves insulin resistance, which is clinically represented by the metabolic syndrome. Hyperglycemia in diabetes—both types 1 and 2—increases cardiovascular risk due to endothelial lesions. Control of all risk factors, including lipids, hypertension, and blood glucose are important to decrease the risk of cardiovascular disease. With particular regard to blood glucose, the UKPDS study (United Kingdom Prospective Diabetes Study) showed that early intensive glycemic control was essential in the reduction in cardiovascular disease. A decrease in mortality observed with glucagon-like peptide-1 (GLP-1) analog use is probably due to a reduction in body weight; findings for empagliflozin still remain unclear. ■ *Heart Metab*. 2017;73:37-39

Keywords:

Type 2 diabetes (T2DM) is related to an increased cardiovascular risk, and the main reason for this is thought to be insulin resistance, which is clinically represented by metabolic syndrome. Metabolic syndrome manifests as an association of symptoms and signs, such as hypertension with blood pressure over 130/85 mm Hg, triacylglycerols higher than 150 mg/dL, high-density lipoprotein levels under 40 mg/dL for men and under 50 mg/dL for women, fasting blood glucose greater than 100 mg/dL, or established T2DM and an abdominal circumference greater than 94 cm for men and greater than 80 cm for women. Of those five signs, the presence of two or more determines a diagnosis of metabolic syndrome.[1] Recently, studies have shown an increased incidence of cardiovascular disease in patients with metabolic syndrome, and added to this, the association of altered blood glucose levels may lead to a further increase in cardiovascular risk.[1] More than half of the patients with T2DM are considered obese and to have metabolic syndrome.[1]

Hyperglycemia observed both in diabetes type 1 and 2 already increases the cardiovascular risk due to endothelial lesions. Recently, Ceriello et al published possible reasons for why patients with unsatisfactory glycemic control over a long period of time do not benefit from better metabolic control.[2] These authors believe that oxidized advanced glycated end products (AGEs) would form as a result of an increase in mitochondrial reactive oxygen species, or ROS. This could modify proteins of the respiratory chain that are encoded by mitochondrial deoxyribonucleic acid (DNA), which—after this damage—lead to persistent formation of ROS independently of hyperglycemia; ROS represent the main factor responsible for AGE formation.[2] It is known that the

presence of ROS is the triggering factor behind development of diabetes complications, both macro and micro, due to endothelial injury.[2]

However, in an approximately 23-year retrospective comparison of patients with type 1 diabetes mellitus (T1DM) and T2DM, diagnosed at the same age (15 and 30 years old), patients with T2DM presented with a higher incidence of macro and microvascular disease and had a higher mortality.[3]

Regarding cardiovascular coronary dysfunction, Bonamichi et al revealed through intravascular ultrasound that hyperglycemia plays an important role in the development of atherosclerotic disease in patients with metabolic syndrome and may lead to a worsening of the pathology.[4]

The control of all risk factors, including lipids, hypertension, and blood glucose, plays an important role in decreasing cardiovascular disease risk. Particularly with blood glucose, the UKPDS study (United Kingdom Prospective Diabetes Study) was effective in demonstrating that early intensive glycemic control is essential to reduce cardiovascular disease.[5] The results of UKPDS 80, a trial that evaluated the same UKPDS outcomes published in 1998, demonstrated that the patients that benefited most in terms of prevention of heart attack and all-cause mortality were the patients in the intensive treatment group.[5]

Cardiovascular safety of hypoglycemic medications

Cardiovascular safety studies performed with hypoglycemic medications for T2DM were and are important, not just to evaluate the primary outcomes related to cardiovascular disease, but also to establish and evaluate possible side effects, as well as benefits, of those medications.

With regard to dipeptidyl peptidase-4 (DPP-4) inhibitors, the studies that have been thus far published, such as SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus – Thrombolysis In Myocardial Infarction),[6] EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care),[7] and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin),[8] have demonstrated cardiovascular safety. However, they have not shown significant decreases in the complications related to T2DM.

The ADVANCE study (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) also demonstrated cardiovascular safety with gliclazide use in patients with T2DM and established cardiovascular disease.[9] The results are important for the differentiation of gliclazide from other medications in terms of cardiovascular safety.[9]

After the ADVANCE study, patients were followed-up for approximately 6 years in the ADVANCE-ON (ADVANCE Observational) trial. Glycated hemoglobin in both ADVANCE and ADVANCE-ON studies was established to be an average of 7.4%, suggesting methodological importance, leading us to conclude that the intensive glucose control at baseline was the main difference.[9]

Recently, results of cardiovascular outcomes trials (CVOTs) were published for two classes of medications. Cardiovascular safety of GLP-1 analogs was shown, with a decrease in mortality in the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results)[10] and a decrease in major adverse cardiac events (MACE) in the SUSTAIN trial (Trial to Evaluate Outcomes with Semaglutide in Subjects with Type 2 Diabetes).[11] Sodium-glucose cotransporter-2 (SGLT2) inhibitors were shown to reduce mortality and MACE in the EMPA-REG OUTCOME trial (Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) with empagliflozin, though there was no reduction in cardiovascular events.[12]

We conclude that treatment for cardiovascular disease in patients with T2DM should be sought from the first day of diabetes diagnosis, with intensive glycemic control, lipid control through use of statins, and hypertension control. The decrease in mortality observed with GLP-1 analogs is probably due to a reduction in body weight, whereas the findings of the empaglifozin study remain unclear. ■

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