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COMMON RISK FACTORS OF HEART DISEASES AND DIABETES

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Annotation:

Heart and vascular disease often go hand-in-hand with diabetes. People with diabetes are at a much greater risk for heart attack, stroke, and high blood pressure. Other vascular problems due to diabetes include poor circulation to the legs and feet. Unfortunately, many cardiovascular problems can go undetected and start early in life.

Keywords: *risk factors, lipid, lipoprotein, hyperglycemia, insulin, obesity, hypertension.*

Introduction

People with diabetes often experience changes in the blood vessels that can lead to cardiovascular disease. In people with diabetes, the linings of blood vessels may become thicker, making it more difficult for blood to flow through the vessels. When blood flow is impaired, heart problems or stroke can occur. Blood vessels can also suffer damage elsewhere in the body due to diabetes, leading to eye problems, kidney problems, as well as poor circulation to the legs and feet.

Metabolic Risk Factors

As a result of demographic, social, lifestyle, and/or genetic risk factors, "metabolic" risk factors act as the first measurable alert of increased CVD risk. Blood markers (of glycemia, lipoproteins, and inflammation), blood pressure, and BMI are all highly predictive of cardiovascular risk and are frequently comorbid. As a result, risk stratification schemes attempt to integrate as many metabolic factors into their risk estimates as possible.

Hyperglycemia and Insulin

Diabetes, as defined by measures and degree of hyperglycemia, is widely accepted as a high-risk state for CVD. Prior to the contemporary definitions for diabetes, the MRFIT cohort followed 347,978 men age 35–57 years at high risk for CHD for an average of 12 years to determine CVD

mortality. Among 5,163 men who reported taking medication for diabetes (as the definition of diabetes), 1,092 men died; 603 of those deaths were due to CVD. Absolute risk for CVD death was three times higher for those with versus without diabetes even after adjustment for age, race/ethnicity, income, serum cholesterol, systolic blood pressure, and number of cigarettes smoked per day. The presumed conclusion from this study was that hyperglycemia was the major driver of CVD risk. Following this presumption, much debate ensued as to whether diabetes defined by FPG compared to 2-hour post-challenge oral glucose tolerance test (OGTT) is more closely related to cardiovascular risk. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study group analyzed individual data from 22 European, 2 Japanese, and 1 American cohorts, which included 29,714 adults (without a diagnosis of diabetes) who were followed for an average of 11 years. The study was conducted to determine whether the glucose association with CVD was linear or showed a threshold effect and whether it was independent of classic CHD risk factors. In the pooled analysis for fatal CVD, a J-shaped association was found with a threshold effect for FPG (97.2 mg/dL [5.39 mmol/L]) and a linear association with 2-hour post-challenge glucose. Risk was increased at blood glucose levels less than those thought to be diagnostic of diabetes. This particular analysis found the 2-hour glucose was a stronger CVD risk factor than FPG. With the declining popularity of the OGTT, the Emerging Risk Factors Collaboration conducted a meta-analysis of 102 prospective studies seeking to address uncertainties about the magnitude of associations of diabetes and fasting glycemia with the risk of CHD. Individual records from 698,782 people without known vascular disease who had 52,765 incident fatal or first-ever nonfatal vascular events during 8.49 million person-years at risk were included. Overall, the risk for CHD was about twofold greater in adults with diabetes at baseline compared to those without. These hazard ratios did not change appreciably after further adjustment for lipid, inflammatory, or renal markers. Hazard ratios for CHD were higher in women than in men, higher at age 40–59 years than at ≥70 years, and higher for fatal than nonfatal CVD. FPG had a U- or J-shaped association with vascular risk, with no significant associations in the normoglycemic range between 3.90 mmol/L (70.3 mg/dL) and 5.59 mmol/L (100.7 mg/dL). Compared with FPG concentrations of 3.90–5.59 mmol/L, hazard ratios for CHD were: 1.11 (95% CI 1.04–1.18) for 5.60–6.09 mmol/L (100.9–109.7 mg/dL) and 1.17 (95% CI 1.08–1.26) for 6.10–6.99 mmol/L (109.9–126 mg/dL), showing a significant, graded risk below FPG-defined diabetes.

In 2010, the American Diabetes Association (ADA) advocated the use of the A1c for diagnosis of both diabetes and prediabetes. Accordingly, interest in A1c as a marker of CVD risk ensued. Since this time, a number of population studies have demonstrated residual CVD risk across the A1c range after adjustment for known CVD risk factors, including below the threshold for A1c-defined diabetes. For example, after adjustment for age, sex, waist circumference, history of CVD, smoking, hypertension, and dyslipidemia in a large U.S. cohort, A1c 5.5%–6.0% (37–42 mmol/mol) versus A1c <5.5% was associated with a 25% higher risk of CHD and 16% higher risk of stroke that further increased to 88% and 119% higher for CHD and stroke, respectively, for A1c 6.0%–6.5% (42–48 mmol/mol). Notably, the continuous relationship between A1c and CVD is not unique to the United States. Consistent findings have been reported in the United Kingdom, Australia, India, and in meta-analyses spanning a wide range of ethnic groups.

Given the limitations of the A1c to accurately measure glycemia in some populations, non-A1c markers of ambient glycemia (i.e., glycated albumin, 1,5-anhydroglucitol, and fructosamine) have gained some traction in clinical medicine. A post hoc analysis of the Atherosclerosis Risk in Communities (ARIC) study looked at the predictive value of these glycemic biomarkers for CVD in 10,373 participants followed from 1990–1992 until 2012. Major findings revealed an association of all three—glycated albumin, 1,5-anhydroglucitol, and fructosamine—with CVD but only at their highest quintile blood concentrations and only in people with diabetes, whether diagnosed by FPG or A1c. No association was seen with these glycemic markers and CVD in people without diabetes,

corroborating earlier findings. The well-established fact that hyperglycemia, however measured, most often occurs in the setting of insulin resistance has led to speculation that insulin resistance, rather than hyperglycemia, drives CVD risk. Proving this hypothesis has been less than straightforward. Unlike glycemia, insulin resistance is difficult to measure outside of a research setting. Early reports linking hyperinsulinemia to CVD were debunked by larger, contemporary trials controlling for confounding variables, although some disagreement remains. Many attribute contradictory findings to lack of standardization in the insulin assay, with many assays failing to discriminate between insulin and proinsulin or note whether the sample was taken in the fasted or fed state. Collectively, there is some indication that proinsulin, but neither fasting nor nonfasting insulin, associates with increased risk for CVD, albeit a marker of beta cell failure rather than insulin resistance. A single study using the intravenous glucose tolerance test (IVGTT) in conjunction with the minimal model demonstrated a 56% increase in coronary artery disease when comparing insulin sensitivity in the 75th versus 25th percentiles, even after adjusting for cardiovascular risk factors. The gold-standard test for assessment of insulin sensitivity—the hyperinsulinemic-euglycemic clamp—has yet to be tested as a predictor of CVD risk.

Lipids and Lipoproteins

Type 2 diabetes and insulin resistance are associated with abnormalities in circulating lipids, including elevated triglycerides and small, dense LDL particles, as well as low concentrations of HDL-C. These abnormalities in circulating concentrations of lipids often precede the diagnosis of type 2 diabetes. For a given concentration of LDL-C, the lipoprotein particles tend to be smaller and denser in patients with type 2 diabetes than in patients without diabetes. Patients with type 2 diabetes tend to have higher triglyceride and lower HDL-C concentrations than patients without diabetes, and until recently, there has been disagreement as to whether triglycerides or HDL-C play a causal role in the development of ASCVD. Large observational studies have noted an association between triglyceride concentrations and cardiovascular events. In a comparison of individuals in the top third with those in the bottom third of usual log-triglyceride values, the adjusted odds ratio (OR) for CHD was 1.57 (95% CI 1.10–2.24) in the EPIC-Norfolk study and 1.76 (95% CI 1.39–2.21) in the Reykjavik study. However, the prevalence of diabetes at baseline in the two cohorts was low (2% and 3%, respectively). After adjusting for baseline values of established risk factors, including a history of diabetes, the strength of these associations was attenuated but remained statistically significant. Mendelian randomization studies are consistent with the hypothesis, but do not prove, that triglycerides or triglyceride-rich remnant lipoprotein particles cause atherosclerosis, even when accounting for LDL-C concentrations. As discussed in detail below, therapies to lower LDL-C concentrations have demonstrated important reductions in major adverse cardiovascular event (MACE) rates. Therapies directed at improving HDL-C and triglyceride concentrations have had more mixed success.

Hypertension

The CDC estimates that 69% of patients with type 2 diabetes have hypertension. Just as dyslipidemia can precede the diagnosis of diabetes, so too can the diagnosis of hypertension precede diabetes. As might be anticipated, patients with type 2 diabetes are also at elevated risk of developing hypertension. An epidemiologic analysis of data from the United Kingdom Prospective Diabetes Study (UKPDS) suggests an increase in both macrovascular and microvascular events with increases in systolic blood pressure in patients with diabetes, as well as a substantially elevated risk of HF and peripheral artery disease (PAD) (including amputation or death from PAD). These data have led the American Heart Association (AHA) to recommend a lower blood pressure treatment goal (<130/80 mmHg) in patients with diabetes with the goal of improving macrovascular and microvascular outcomes. However, recommendations about which patients to treat aggressively, and which to treat less aggressively, have historically differed among major

professional organizations, although recent guidelines from the ADA reflect greater concordance with those from the AHA. Recommendations have differed in part because of concern about potential adverse effects of antihypertensive therapy in patients with diabetes and because of a lack of clarity from clinical trial data.

Obesity

Obesity was the first recognized and remains the strongest single risk factor for type 2 diabetes, as the obesity epidemic that began in the United States in the early 1980s was closely associated with the epidemic of diabetes. A subsequent epidemic of CVD was predicted, but thus far, the amount of CVD in the United States continues to decline overall in both sexes and in most race/ethnicity groups. The paradox of decreasing prevalence in CVD despite increasing prevalence of obesity—irrespective of diabetes status—has been attributed to improved lifestyle, use of better lipid-lowering and blood pressure medications, smoking cessation, and more revascularization surgery. Alternate hypotheses for the lack of increase in CVD prevalence despite the increase in obesity prevalence include uncertainties as to the measure of adiposity used in trials (i.e., BMI, waist circumference, or waist-to-hip ratio), lack of data on how change in any measure of adiposity predicts CVD events, and whether adiposity increases cardiovascular risk independent of frequently coexistent cardiovascular risk factors. BMI has been the most widely used measure of adiposity, when examining the association between adiposity and CVD, with separate "at-risk" cut points set for Caucasian and Asian populations, but it has also been the most openly criticized. One large, multinational case-control study found that waist-to-hip ratio was three times more strongly related to acute MI than was BMI. Other proponents advocate measuring waist circumference, citing its similar performance as waist-to-hip ratio in both the Nurses' Health Study and a combined analysis of 15 prospective cohort studies. Lack of agreement as to which measure is the correct measure of adiposity is further magnified when discussing the lack of data on how long-term change in each measure relates to CVD risk.

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