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Heart Disease and Diabetes Incidence and Clinic Biomarkers

Azizova Noilaxon Saidolimxon qizi [1]

Annotation: Heart disease remains a major cause of morbidity and mortality among individuals with type 2 diabetes. Meta-analyses have demonstrated a pooled relative risk for incident coronary heart disease (CHD) that is approximately twofold higher overall in adults with diabetes compared to those without diabetes. In studies that further stratify results by sex, the relative risk of CHD is higher in women than men in the presence of diabetes.

Key words: coronary heart disease, lipoprotein, diabetes, C-Reactive Protein, High-Sensitivity Cardiac Troponin, B-Type Natriuretic Peptides.

Classic heart disease risk markers have been clearly demonstrated to be important determinants of heart disease in diabetes, including elevated low-density lipoprotein cholesterol, elevated blood pressure, smoking, and elevated triglycerides and low high-density lipoprotein cholesterol. Obesity is an important risk factor for type 2 diabetes but has not consistently been shown to have an independent association with heart disease, possibly because obesity is in the causal pathway between these risk factors and heart disease development. However, several studies indicate that the excess prevalence of heart disease in diabetes is not fully accounted for by measured classic cardiovascular disease risk factors. In addition, novel biomarkers have been found to either add no or only modest incremental significance in the prediction of heart disease. The association between fasting glucose and heart disease displays a J-shaped curve in several studies. Glycosylated hemoglobin also has a graded association with heart disease. The association between insulin resistance and heart disease is inconsistent, at least in part because of methodologic differences among studies. Other important risk factors include lifestyle factors, such as physical activity, smoking, diet, and social determinants of health, such as food insecurity, access to health care, or poverty. Clinical trials involving modification of cardiovascular risk factors in diabetes have helped to clarify their roles in heart disease development. Clinical trials focusing on weight reduction through an intensive lifestyle intervention specifically in people with diabetes have not demonstrated benefit in cardiovascular events despite improvement in risk factors. Whether improvement of glycemic control reduces heart disease has long been a central question, since older trials had not consistently demonstrated benefit. By contrast, lipid-lowering clinical trials have shown that statin treatment, in both secondary as well as primary prevention trials, significantly reduces atherosclerotic heart disease with a similar risk reduction to that seen in people without diabetes. Large randomized trials have demonstrated that highly purified eicosapentaenoic acid ethyl ester significantly reduces risk of ischemic events. Trials of more intensive compared to standard blood pressure control in people with diabetes did not generally find that achieving a lower goal leads to a reduction in cardiovascular events overall. The benefits of aspirin in reducing serious vascular events have been demonstrated in trials of people with diabetes, but these benefits are largely counterbalanced by an increase in major bleeding events.

A biomarker is a biological marker that indicates the presence of a disease or the risk for a disease state. Clinically useful biomarkers are ones that can be measured, improve diagnostic or prognostic performance, and aid in the clinical management of patients by guiding the initiation, duration, or intensity of therapy. As imaging biomarkers (i.e., subclinical atherosclerosis) are discussed in another section, this section focuses on circulating blood biomarkers, excluding lipid biomarkers and glycemic markers, which are also discussed in other sections. A large number of biomarkers have been

[1] Assistant of the " Department of Fundamentals of Pathology and Forensic Medicine" of CAMU International Medical University

examined for their utility in CVD (cardiovascular disease) risk assessment, but for space limitation, only the ones most commonly used for CVD risk assessment are described, including hsCRP, high-sensitivity cardiac troponin (hs-cTn), B-type natriuretic peptides (BNP).

C-Reactive Protein

C-reactive protein is a marker of inflammation, and hsCRP levels are higher among individuals with obesity, insulin resistance, and diabetes. Among women without diabetes, higher CRP levels are independently associated with fasting insulin levels. Furthermore, hsCRP levels predict the risk for incident type 2 diabetes, implicating the role of low-grade inflammation in diabetes pathogenesis. However, associations of inflammation with diabetes risk have been attenuated after accounting for BMI, suggesting adiposity may be mediating this relationship. In addition to predicting future type 2 diabetes risk, elevated levels of hsCRP predict incident ASCVD and improve risk prediction independently of the lipid profile. The Reynolds Risk Scores for prediction of CVD, which incorporate hsCRP in their equations, improve risk discrimination over traditional risk factors alone. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) enrolled apparently healthy individuals without CVD or diabetes, who had LDL-C levels <130 mg/dL (<3.37 mmol/L) but elevated hsCRP levels ≥2 mg/L, and found that statin treatment reduced MACE by 44% (HR 0.56, 95% CI 0.46–0.69) compared to placebo. This pivotal trial provided key evidence demonstrating the benefit of statin therapy in patients with elevated hsCRP levels. Although this study excluded persons with diabetes, 41% of participants did have the metabolic syndrome, and the benefit of statin therapy was seen across metabolic syndrome groups. Therefore, the 2019 American College of Cardiology (ACC)/AHA primary prevention guideline considers elevated hsCRP ≥2 mg/L to be a “risk-enhancing” factor that would favor the initiation of statin therapy among individuals at borderline or intermediate risk. However, as persons with diabetes who are age ≥40 years are already recommended for statin therapy, the role of hsCRP assessment for guiding treatment decisions in this population is unclear.

High-Sensitivity Cardiac Troponin

Cardiac troponin is a protein found in cardiac myocytes that is released in the setting of myocardial injury. Although its clinical utility is established in the diagnosis of MI, its utility in predicting risk of incident ASCVD risk among asymptomatic individuals has been increasingly recognized. The development of high-sensitivity troponin assays (i.e., hs-cTnT and hs-cTnI) permits the detection of circulating troponin at much lower thresholds, on the order of ng/L, as early markers of subclinical myocardial injury. In patients with type 2 diabetes and chronic, stable coronary artery disease who were enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial, hs-cTn concentration was an independent predictor of death from cardiovascular causes, MI, or stroke; however, among patients with abnormal hs-cTn concentrations, random assignment to prompt revascularization compared with medical therapy alone did not result in a significant reduction in the rate of the composite cardiovascular endpoint. In general population cohorts, elevated levels of hs-cTn have been independently associated with future ASCVD events even after accounting for traditional CVD risk factors. The addition of hs-cTn improves risk prediction compared to other risk prediction equations, such as the pooled cohort equations (PCE) and the Framingham Risk Score. Furthermore, in a primary prevention clinical trial, statin therapy significantly reduced hs-cTn over 5 years compared to placebo, and participants who experienced the greatest reduction in hs-cTn had a fivefold lower risk of coronary events compared to those whose hs-cTn increased. Cardiac troponin also predicts risk among individuals with established diabetes. Among middle-aged adults with diabetes in the ARIC study, subclinical elevation of hs-cTn was independently associated with increased risk of incident ASCVD, HF, and all-cause mortality. In fact, persons with diabetes with hs-cTn above the 90th percentile had similar risks as individuals with established CVD. This finding suggests that the use of hs-cTn can help improve risk stratification in persons with diabetes and potentially guide clinical management, such as intensification of preventive therapies. Nevertheless, current guidelines do not specifically endorse or recommend the use of hs-cTn in risk assessment or management of asymptomatic individuals.

B-Type Natriuretic Peptides

BNPs are secreted from cardiac myocytes in response to myocardial wall stress, which can occur in the setting of volume expansion and/or pressure overload. While normally BNP plays a favorable physiologic role by promoting vasodilation and natriuresis, its elevation in the blood signals compensatory adaptation to a pathological state, such as subclinical or clinical HF, left ventricular hypertrophy, or myocardial ischemia. ProBNP is the prehormone that is cleaved to the active hormone BNP and also to the N-terminal pro B-type natriuretic peptide (NT-proBNP). Both BNP and NT-proBNP levels are used clinically in the evaluation of patients with suspected HF. However, even among asymptomatic individuals free of clinical ASCVD or HF, elevated NT-proBNP levels are associated with an increased risk of incident CVD, hospitalizations for HF, and cardiovascular mortality. In patients with established diabetes, higher levels of BNP predict future CVD and mortality. Interestingly, higher NT-proBNP and BNP levels are associated with lower risk of incident diabetes, which actually suggests a favorable role of natriuretic peptides for type 2 diabetes prevention. Mendelian randomization studies are consistent with the hypothesis that the BNP locus may have a causal role in the development of diabetes. Similar to hs-cTn, current guidelines do not specifically endorse or recommend the use of natriuretic peptide measurement for risk assessment in asymptomatic individuals. However, this biomarker does have utility in the diagnosis of HF. Of note, BNP levels are paradoxically lower in persons with obesity compared to those without obesity, adding to the challenge of diagnosing HF with preserved ejection fraction among individuals with obesity.

In conclusion, despite intensive management of cardiovascular risk factors, the high risk for heart disease among people with diabetes remains a major health concern. Importantly, over the past few years, an increasing number of therapies have become available to reduce cardiovascular risk in people with type 2 diabetes.

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