TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

In diabetes, treat hidden heart disease

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ABSTRACT

Both diabetic and prediabetic patients have abnormal vascular reactivity and should be considered to have occult cardiovascular disease. Angiotensin-converting-enzyme (ACE) inhibitors are particularly beneficial in diabetes because they reduce the incidence of both cardiovascular events and diabetes-related complications. In prediabetic patients, ACE inhibitors also reduce the risk of a new diagnosis of type 2 diabetes. Managing hypertension is even more beneficial for diabetic patients than for nondiabetic patients. To further reduce the risk of heart disease in patients with diabetes or prediabetes, dyslipidemia should also be treated aggressively.

DIABETES is not only a metabolic disease, but also a vascular disease. Diabetic patients, even those with no symptoms of heart disease, have abnormal vascular responses to stress that show that they have occult vascular disease. These abnormal reactions are also found in prediabetic patients (those with impaired glucose tolerance, hyperinsulinemia, and obesity). Thus, we must assume the presence of incipient heart disease in all diabetic and prediabetic patients and treat them accordingly.

In this article, we discuss the mechanisms in common between heart disease and diabetes, and we review evidence from clinical trials about how patients with diabetes benefit from lipid reduction and antihypertensives, particularly angiotensin-converting enzyme (ACE) inhibitors.

*The author has indicated that she has received grant or research support from the Bristol-Myers Squibb and Parke-Davis corporations, and serves as a consultant and on the speakers' bureau for Merck and Co. Her lecture was supported by a grant from Parke-Davis.

PATIENTS WITH DIABETES ARE AT HIGH RISK

Diabetes is linked with vascular disease in many ways. Microvascular complications of diabetes include nephropathy and retinopathy. Diabetes is one of the major risk factors for heart disease, and cardiovascular disease is the leading cause of death among people with type 2 diabetes.

Among patients with coronary heart disease, diabetic patients are far more likely to die than nondiabetic patients. Diabetes eliminates women's estrogen-mediated protection against heart disease. A diabetic patient with no history of heart disease has just as high a risk of myocardial infarction as does a nondiabetic patient with a previous myocardial infarction.[1]

Diabetic patients have occult coronary artery disease

MECHANISM LINKS HEART DISEASE AND DIABETES

At the physiological level, the link between cardiovascular disease and diabetes is oxidative stress (see OXIDATIVE STRESS LINKS DIABETES AND HEART DISEASE, page 808). Oxidative stress, an imbalance between antioxidants and damaging oxidizing agents, can impair the function of the vascular epithelium, destroying its ability to balance vasodilation and vasoconstriction.

Oxidative stress can be caused by a number of heart disease risk factors, including hypertension, smoking, and high LDL cholesterol; as a result, all of these factors impair vascular responsiveness even in persons without

Oxidative stress links diabetes and heart disease

THE VASCULAR ENDOTHELIUM was once thought to be a pipeline, and cardiologists merely plumbers. Today, we recognize the endothelium as a dynamic organ that actively regulates vasoconstriction through autocrine and paracrine routes (FIGURE 1). As a result, cardiology has become more like endocrinology.

A PREDOMINANCE OF VASOCONSTRICTORS

The endothelium produces both vasodilators such as nitric oxide and vasoconstrictors such as endothelin-1. In addition, it contains angiotensin-converting enzymes (ACE), which help produce the potent vasoconstrictor angiotensin II.

In healthy people, vasoconstrictors and vasodilators are balanced. A number of diseases, including diabetes, produce oxidative stress—an imbalance between antioxidants and harmful oxidizing free radicals. The result is a predominance of vasoconstrictors, many of which promote other processes that can damage the endothelium, including thrombosis, inflammation, and oxidation.

Damaged endothelial cells further promote inflammation by expressing adhesion molecules, which attract adhering platelets and leukocytes. Angiotensin II also promotes the degradation of nitric oxide and destabilizes existing atherosclerotic plaques, increasing the risk of plaque rupture and myocardial infarction.

Diabetes and insulin are integrally involved in the balance. Insulin itself is a vasodilator, and conversely, vasoconstriction may contribute to insulin resistance by reducing blood flow to insulin-sensitive tissues that take up circulating glucose.

Insulin resistance is associated with several cardiovascular risk factors implicated in endothelial damage: hypertension, high levels of triglycerides and of small dense LDL particles, which are highly susceptible to oxidative damage, and elevated circulating plasminogen activator-inhibitor 1 (PAI-1), a prothrombotic agent. Hyperinsulinemia is also an independent risk factor for atherosclerosis.

ACE INHIBITORS AND OXIDATIVE STRESS

The beneficial effects of ACE inhibitors in diabetes may be related to their effect on oxidative stress and vasodilation. ACE is the enzyme that degrades bradykinin, and so ACE inhibition increases levels of bradykinin, a vasodilator known to promote insulin-mediated glucose uptake. In addition, the ability of ACE inhibitors to increase nitric oxide levels reduces oxidative stress and improves systemic blood flow; this could directly benefit the pancreas and could also promote glucose uptake in skeletal muscle.

On the other hand, others have suggested that ACE inhibition may merely obviate patients' need for beta-blockers, which have recently been implicated in increasing the risk of developing diabetes.

overt coronary artery disease. The vascular abnormalities can be assessed by measuring the response to acetylcholine and methacholine, which normally increase blood flow by increasing endothelial production of the vasodilator nitric oxide. In persons with either coronary disease or risk factors, acetylcholine injections produce a paradoxical vasoconstriction, indicating severe endothelial damage in the coronary arteries.[2]

Diabetes is also a source of oxidative stress, and notably, diabetic patients with no history of coronary artery disease show blunted vascular dilatation in response to methacholine.[3] This provides part of the explanation for why type 2 diabetes increases a patient's risk of coronary heart disease mortality three-fold or four-fold.

RISK IN PREDIABETIC PATIENTS

The risk of coronary heart disease is also elevated in patients with impaired glucose tolerance (prediabetes), defined either as a fasting glucose level of 110 to 125 mg/dL or as a postprandial glucose level of 140 to 200 mg/dL. Within 5 years, between 30% and 50% of these prediabetic patients will develop type 2 diabetes.

However, even before developing overt

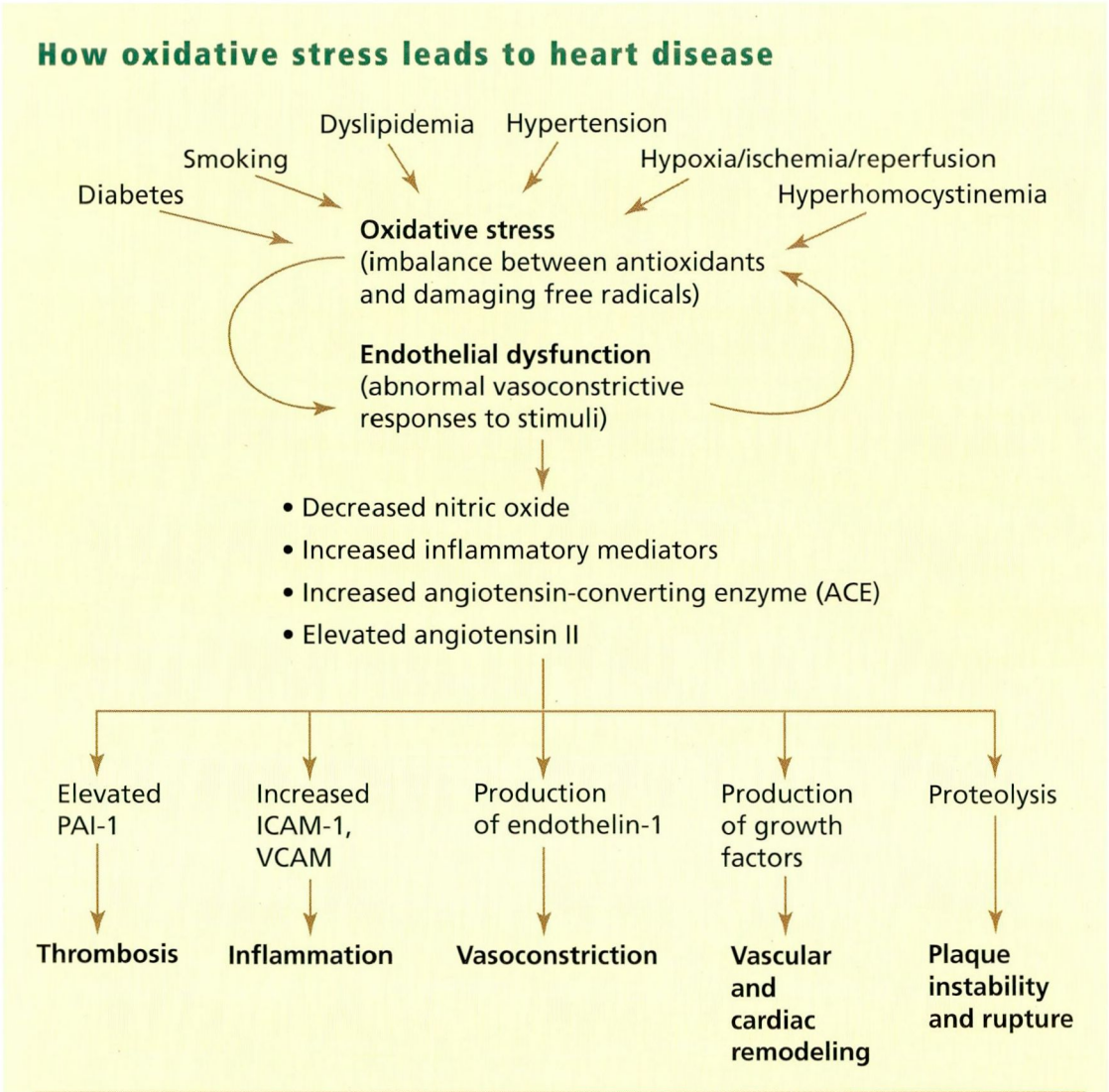

FIGURE 1. Scheme of how oxidative stress and endothelial dysfunction work synergistically to lead to heart disease in patients with diabetes. PAI-1 = plasminogen activator inhibitor 1; ICAM-1 = intracellular adhesion molecule 1; VCAM = vascular cell adhesion molecule

Insulin resistance impairs vascular responsiveness

diabetes, prediabetic patients already have a two-fold or three-fold increased rate of coronary artery disease mortality.

HYPERINSULINEMIA LINKED WITH VASCULAR DISEASE

In addition, obese patients with hyperinsulinemia may have signs of both insulin resistance and vascular disease, even if their glucose tolerance is normal.[4] When insulin is infused into the femoral artery of lean subjects, muscle uptake follows a clear dose-response pattern; that is, more insulin leads to more insulin uptake. However, in obese but otherwise healthy subjects, higher insulin doses are not quickly absorbed, indicating insulin resistance.

Insulin itself stimulates nitric oxide production, and in lean subjects it increases blood flow by vasodilation. However, insulin produces a far smaller degree of vasodilation in

nondiabetic obese subjects, revealing that they already have endothelial cell dysfunction.

INSULIN RESISTANCE ALONE CAUSES VASCULAR ABNORMALITIES

In a recent small study,[5] we used the euglycemic clamp technique to identify the most insulin-sensitive and the least insulin-sensitive (or most insulin-resistant) subjects in a group of healthy, nondiabetic Mexican-Americans. The insulin-sensitive subjects were of average weight, with a mean body mass index (BMI) of 23 kg/m^2, but the insulin-resistant subjects were obese, with an average BMI of 35 kg/m^2. The insulin-resistant subjects also had slightly lower HDL, higher triglycerides, higher fasting insulin, and higher (but still normal) fasting glucose levels. None of the subjects smoked or had hypertension, diabetes, or hypercholesterolemia.

In these two groups, we measured endothelial-dependent blood flow in the coronary artery by cold-pressor testing—ie, placing the hand in cold water for 2 minutes to induce systemic vasoconstriction, then taking it out to induce endothelial-dependent vasodilation. In the insulin-resistant group, coronary artery response to cold-pressor testing was only 50% of the response in the insulin-sensitive subjects, revealing a clear abnormality in these otherwise young and healthy people. These findings confirm that we should be concerned about diabetes, heart disease, and oxidative stress in obese patients even before they become diabetic.

In diabetes, the NKF recommends a BP goal of 130/80

TRIAL RESULTS: ACE INHIBITORS BENEFICIAL IN DIABETES

The Heart Outcomes Prevention Evaluation (HOPE) study[6] showed that the ACE inhibitor ramipril was beneficial for all patients at high risk for coronary artery disease, but it had particularly marked benefits for diabetic patients. Ramipril not only reduced their chances of cardiac events, nephropathy, and mortality, but also reduced the incidence of diabetes-related complications.

Ramipril may even prevent diabetes. The HOPE trial's nondiabetic patients were at high risk of type 2 diabetes; many were obese and unable to exercise because of their coronary artery disease. Many probably had impaired glucose tolerance, a first step toward the development of diabetes. Among these patients, ramipril reduced the incidence of new diagnoses of diabetes by 44%.

The Captopril Prevention Project (CAPPP)[7] also showed that an ACE inhibitor, captopril, could reduce the incidence of new-onset diabetes.

Additional evidence in favor of ACE inhibitors comes from the **Trial on Reversing Endothelial Dysfunction (TREND study)**,[2] showing that 6 months of treatment with an ACE inhibitor can restore impaired acetylcholine-stimulated vasodilation.

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial[8] was stopped early because the ACE inhibitor enalapril was showing a clear benefit over the calcium channel blocker nisoldipine. The 235 diabetic patients in the nisoldipine group experienced 25 myocardial infarctions, whereas the 235 patients receiving enalapril had only 5. Cardiovascular mortality in the nisoldipine group was twice that in the enalapril group.

The BANFF trial[9] suggested that quinapril (an ACE inhibitor) may be better for improving endothelial-dependent blood flow than are enalapril (another ACE inhibitor), losartan (an angiotensin II receptor antagonist), or amlodipine (a calcium channel blocker). This is important for diabetes, which impairs endothelial-dependent blood flow. The differences between the drugs raise the possibility that quinapril's tissue-penetrating abilities make it more cardioprotective.

TRIAL RESULTS: HYPERTENSION AND DIABETES

Treating hypertension in patients with diabetes reduces cardiovascular risk even more than treating hypertension in other patients.

The Hypertension Optimal Treatment (HOT) trial showed that the lower a diabetic patient's blood pressure, the lower the risk of cardiovascular events.[10] In general, blood pressure should be kept even lower in diabetic patients than in patients with essential hypertension. The 1998 report of the Joint National

Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (the JNC VI) set the target blood pressure for diabetic patients at 130/85 mm Hg, and the target for diabetes accompanied by proteinuria at 125/75 mm Hg.[11] Results of the **UK Prospective Diabetes Study (UKPDS)**[12] supported these recommendations.

A recent consensus statement from the National Kidney Foundation recommended a blood pressure goal of 130/80 mm Hg based on trials that used reductions in cardiovascular events and proteinuria as endpoints.[13] Patients with diabetes typically need three or four drugs to reach these blood pressure goals. Antihypertensive agents that increase glucose levels should be avoided.

Although the JNC VI recommended alpha-blockers as a good option for lowering blood pressure in diabetic patients,[11] the **ALLHAT trial**[14] identified an increased incidence of heart failure with alpha-blockers compared with diuretics; therefore, alpha blockade is no longer recommended as first-line therapy for hypertension in diabetes.[13]

Other measures for cardiovascular health in diabetes

Controlling dyslipidemia also improves endothelial function. In patients with high LDL, lovastatin improves vascular response to acetylcholine.[15] Clinical studies suggest that statins improve endothelial function and protect all patients, especially those with diabetes or impaired glucose tolerance, from cardiovascular events and death.[16]

Rigorous glycemic control through sulfonylurea drugs or exogenous insulin confers a cardioprotective effect.[12] Metformin may have a greater cardioprotective effect.[12] Thiazolidinediones are protective in animal models of atherosclerosis; their effects in humans require further investigation.

Exercise and good dietary habits should be encouraged not just for glycemic control but also for cardiovascular benefits.

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