Both essential hypertension and diabetes mellitus affect the same major target organs—the brain, the fundi, the heart, and the kidneys. The common denominator of hypertensive/diabetic target organ disease is the vascular tree. Both hypertension and diabetes are well identified risk factors for atherogenesis. Coronary artery disease is much more common in diabetic hypertensive patients than in patients suffering from hypertension or diabetes alone. Typical for the diabetic hypertensive heart are extensive degenerative changes and a greater degree of hypertrophy compared with the nondiabetic hypertensive heart. The combined presence of hypertension and diabetes concomitantly affects glomerular filtration rate and renal blood flow, thereby greatly accelerating a decrease in renal function. Hypertension accelerates the development of diabetic retinopathy; hypertensive/diabetic cerebral disease leads to vascular dementia, transient ischemic attacks, and strokes. A decrease in the hemodynamic and glycemic burden is the primary goal in the management of the hypertensive diabetic patients. Both diuretics and \( \beta \)-blockers have been reported to adversely affect the overall risk factor profile in the diabetic patient. In contrast, the postsynaptic \( \alpha \)-blockers, the calcium antagonists, and the angiotensin-converting enzyme inhibitors have been reported to be either neutral or beneficial with regard to the overall metabolic risk factor profile. The combination of a heart rate lowering calcium antagonist, particularly verapamil, with an ACE inhibitor offers some potential to either prevent or reverse target organ disease associated with hypertension and diabetes. Am J Hypertens 1997;10:198S–201S © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Hypertension, diabetes mellitus, target organ damage, antihypertensive drugs.
malities that often present in diabetic hypertensive patients accelerate atherosclerosis. Plasma levels of lipoprotein have been noted to be elevated in diabetic individuals, particularly those with poor glycemia control. Augmented oxidation of low-density lipoprotein cholesterol and formation of glycated low-density lipoprotein, which enhance foam cell formation, have been observed in diabetic states. Anatomic and functional abnormalities of the vascular endothelium have been described in diabetes mellitus and hypertension. Hyperglycemia activates protein kinase C in endothelial cells, which may enhance vascular tone, permeability, and atherosclerosis. Elevated circulating levels of insulin as exist in type II diabetes in many patients with essential hypertension may contribute either directly or in conjunction with insulin-like growth factor (IGF) to the accelerated atherosclerosis associated with these conditions. Insulin and IGF-1 may exert their atherogenic effects through influences on both vascular endothelial cells and vascular smooth muscle cells. Diabetes mellitus and hypertension are also associated with hematologic abnormalities that encourage thrombosis. Enhanced platelet adhesion and aggregation as well as higher than normal levels of some coagulation factors contribute to the procoagulation state in diabetic hypertensive patients. Diabetes seems to be a specific risk factor for small vessel disease. In contrast, hypertension, at least in its nonmalignant form, seems to affect predominantly the large arteries. Together, the two disorders synergistically damage the arterial tree.

THE HEART

Coronary Artery Disease  Coronary artery disease is much more common in diabetic hypertensive patients than in patients suffering from hypertension or diabetes alone. For all 2,681 men in the PROCAM trial who had none of the three risk factors (that is, hypertension, diabetes, or hyperlipidemia), the coronary artery disease incidence was 6/1,000 in 4 years. In contrast, the incidence of coronary artery disease in those participants who were suffering from hypertension or diabetes was 14 and 15 per 1,000 in 4 years respectively. When both risk factors were present in the same patient, the incidence rate increased to 48 per 1,000.2 Diabetes, and to a lesser extent hypertension, may alter the perception of ischemic pain, leading to a high prevalence of silent ischemia. Melina et al3 found a high prevalence of asymptomatic ST segment depression in diabetic patients with essential hypertension. The number of ST segment depression episodes was significantly related to glycosylated hemoglobin levels, left ventricular mass, and ambulatory systolic and diastolic blood pressure variability and hypertensive peaks.

Diabetic Hypertensive Cardiomyopathy  Experimentally it has been well documented that the coexistence of diabetes and hypertension is associated with myocardial damage. The extensive degenerative changes in the diabetic hypertensive heart may be related to abnormalities in the microcirculation. The most striking microscopic findings of the hypertensive diabetic heart seem to be the distribution of dense interstitial connective tissue throughout the myocardium. Clinical studies with echocardiography also showed an increased left ventricular mass in diabetic hypertensive patients. Grossman et al4 found increased septal and posterior wall thickness in patients with hypertension and diabetes compared with nondiabetic hypertensive patients. Prevalence of left ventricular hypertrophy was 72% in diabetic hypertensive patients and only 32% in the nondiabetic hypertensive patients who had a similar degree of hypertension. Because left ventricular hypertrophy is known to predispose patients with hypertension to cardiovascular morbid and fatal events, the finding of a high prevalence of left ventricular hypertrophy in diabetic hypertensives may partially explain the increased morbidity and mortality in these patients.

THE KIDNEYS

The early phase of hypertensive renal disease is characterized by a normal glomerular filtration rate, a decrease in renal blood flow and, as a consequence, an elevated filtration fraction. Only relatively late in the evolution of the disease can a decrease in glomerular filtration rate be encountered. In contrast, in the diabetic patient the glomerulus is affected from the very beginning. Indeed, hyperfiltration and microproteinuria resulting from glomerular leakage is a hallmark of incident diabetic renal disease. The combined presence of hypertension and diabetes will therefore concomitantly affect glomerular filtration rate and renal blood flow, thereby greatly accelerating a decrease in renal function. Indeed, evidence shows that all levels of untreated hypertension are associated with declining renal function.5 Not surprisingly, therefore, the combined presence of hypertension and diabetes is one of the leading causes of end-stage renal disease in the United States.

THE BRAIN AND RETINA

Ever since the pioneering observations of Keith, Wagener, and Barker, hypertension has been known to affect the ocular fundus. Hypertensive retinopathy consists of narrowing of the retinal arteries, dilatation of the vein crossing phenomena, and in severe cases, papilledema, cotton-wool exudates, as well as star figure in the macula. In contrast to hypertensive reti-
nopathy, diabetic retinopathy is characterized by vascular proliferation. Hence, we are dealing with neovascularization and formation of microaneurysms. Hypertension accelerates the development of diabetic retinopathy. Knowler et al found that in diabetic subjects not taking insulin, the incidence of exudates in those with systolic blood pressure of ≥ 145 mm Hg was more than twice that of those with pressures of < 125 mm Hg. The combination of hypertensive and diabetic retinopathy is often devastating and has been one of the leading causes of blindness in the past. The exact pathogenic and pathophysiologic mechanisms of hypertensive/diabetic cerebral disease are less well documented, although they probably parallel the evolution of retinopathy. The lack of pathophysiologic data notwithstanding, the consequences of the two disorders leading to vascular dementia, transient ischemic attacks, and strokes are well appreciated by the practicing physician.

**PREVENTION AND THERAPY**

A decrease in the hemodynamic and glycemic burden is the primary goal in the management of the hypertensive diabetic patient. This would indicate that antihypertensive drugs should not adversely affect blood sugar control or concomitant risk factors for vascular disease and that pari passu antidiabetic measures should not increase the hemodynamic burden. Both diuretics and β-blockers have been reported to adversely affect the overall risk factor profile in the diabetic patient. In contrast, the post synaptic α-blockers, the calcium antagonists, as well as the angiotensin-converting enzyme (ACE) inhibitors have been reported to be either neutral or beneficial with regard to the overall metabolic risk factor profile. ACE inhibitors, in particular, have been shown to slow down the progress of diabetic nephropathy and to facilitate glycemic control independent from their effects on arterial pressure. Similarly, the heart rate lowering calcium antagonists, specifically verapamil, seem to exert a beneficial effect on diabetic renal disease. ACE inhibitors improve congestive heart failure and reduce recurrent myocardial infarction, congestive heart failure, and cardiac mortality in post-myocardial infarction (MI) patients with low ejection fraction. Verapamil also has been shown to reduce reinfarction rates in post-MI patients. This effect seems to be unique for heart rate lowering calcium antagonists and is not shared by the dihydropyridines. In contrast to this heterogeneity with calcium antagonists, the effect of ACE inhibitors on the remodeling of the heart in the post-MI patient seems to be a class effect. Nevertheless, these considerations make the combination of a heart lowering calcium antagonist with an ACE inhibitor very attractive in the hypertensive diabetic patient. Indeed, Bakris et al in a small short-lasting study, found that the combination of reduced doses of lisinopril—an ACE inhibitor—and verapamil was more effective than either drug alone in attenuating both albuminuria and the rate of decline in glomerular filtration rate. It must be emphasized, however, that the fact that two different drugs, as monotherapeutic agents, are beneficial in a given clinical condition does not necessarily mean that their combination will have an additive or synergistic effect in the long run. Thus, although the combination of an ACE inhibitor with a heart rate lowering calcium antagonist offers a variety of attractive features in the hypertensive diabetic patient, the exact benefits will have to be defined by a prospective, well controlled database.

**SUMMARY**

Hypertension and diabetes both affect the major target organs, the heart, the kidneys, and the brain. The common denominator of hypertensive diabetic target organ disease is the vascular tree. The combined presence of the two disorders in the same patient has devastating consequences, greatly accelerating cardiac, renal, retinal, and cerebral damage. Both calcium antagonists and ACE inhibitors have been shown to be beneficial for arterial hypertension and inert with regard to the overall risk factor profile associated with diabetes. The combination of heart rate lowering calcium antagonist, particularly verapamil, with an ACE inhibitor offers some potential to either prevent or reverse target organ disease associated with hypertension and diabetes.

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