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## Hypertension and Diabetes

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### Abstract

Both essential hypertension and diabetes mellitus affect the same major target organs. The common denominator of hypertensive/diabetic target organ-disease is the vascular tree. Left ventricular hypertrophy and coronary artery disease are much more common in diabetic hypertensive patients than in patients suffering from hypertension or diabetes alone. The combined presence of hypertension and diabetes concomitantly accelerates the decrease in renal function, the development of diabetic retinopathy and the development of cerebral diseases. Lowering blood pressure to less than 130/80 mm Hg is the primary goal in the management of the hypertensive diabetic patients. Beta-blockers have been reported to adversely affect the overall risk factor profile in the diabetic patient. In contrast, calcium antagonists, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been reported to be either neutral or beneficial with regard to the overall metabolic risk factor profile. Combination therapy is usually required to achieve blood pressure goal in diabetic patients. The addition of aldosterone antagonists may be beneficial in patients with resistant hypertension and low levels of serum potassium. Aggressive control of blood pressure, cholesterol and glucose levels should be attempted to reduce the cardiovascular risk of diabetic hypertensive patients.

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### Introduction

The tide of diabetes is rising in the United States and all over the globe, thereby becoming an increasingly powerful threat to global health. In the United States alone, the prevalence of diabetes has doubled from 1990 to the year 2000. The World Health Organization projects that by the year 2025 more than 5% of the world population, i.e. 300 million people will suffer from diabetes. A patient who suffers from type 2 diabetes has a 2–4 times greater risk of death from cardiovascular causes than the patient without diabetes [1]. The most

common cause of dying in the diabetic patient is heart disease. In addition, peripheral vascular disease, end-stage renal disease, blindness and amputations are common co-morbidities in diabetic patients.

Hypertension has been identified as a major risk factor for the development of diabetes. Patients with hypertension are at a 2–3 times higher risk of developing diabetes than patients with normal blood pressure [2]. Hypertension by itself is, of course, a powerful risk factor for cardiovascular morbidity and mortality as established by data from the Framingham cohort more than three decades ago. For any given level of systolic blood pressure, the occurrence of diabetes distinctly increases cardiovascular mortality. Stamler et al. [3] have documented that diabetes in the normotensive patient confers greater risk than a systolic blood pressure between 160 and 170 mm Hg. This observation provoked Haffner and Cassells' [4] observation that the prognosis of diabetes is just as grim as the one of a patient who has suffered an acute myocardial infarction. Of note, while this is true for overall cardiovascular mortality, it does not necessarily mean that diabetes and hypertension are synonymous in affecting the individual components of cardiovascular system. Also, it does by no means follow that specific cardiovascular drugs are equally protective in diabetes and coronary artery disease.

Blood pressure control remains unacceptably low in the general population, but is even lower in the diabetic hypertensive patient [5]. Although controlling the blood pressure is a commendable goal of antihypertensive therapy, treating hypertensive cardiovascular disease in the diabetic patient is more complex than simply achieving blood pressure targets. Recent studies have shown that antihypertensive drug classes have differing effects on the risk of new onset diabetes, on metabolic endocrine surrogate endpoints and possibly on outcome [6]. The present chapter reviews the epidemiology of hypertension and diabetes and discusses clinical findings and gives some recommendations for therapy of the diabetic hypertensive patient.

## **Epidemiology**

Between 1976 and 1988, the prevalence of diabetes (among people age 40–74 years) rose from 11.4 to 14.3% in the USA [7]. Similar increase in the prevalence of diabetes has been described in other parts of the world [8–10]. It is estimated that globally, the number of people with diabetes will rise from 151 millions in the year 2000 to 221 million by the year 2010 and to 300 million by 2025 [11].

The projections of increasing numbers of people with diabetes are driven mainly by the anticipated world population growth, especially amongst the middle-aged and elderly. This spectacular increase in the frequency of type 2

diabetes is being paralleled by a similar alarming increase in obesity [12] which is the major risk factor for type 2 diabetes. Improved nutrition, better hygiene and control of many communicable diseases, have increased longevity. In addition, life-style changes that have been well documented in some countries [13] and include higher fat diets and decreased physical activity contributed to the increase prevalence of type 2 diabetes. The rising prevalence of obesity and type 2 diabetes is also observed in children and is yet another symptom of the effects of globalization and industrialization, with sedentary lifestyle and obesity as the predominant factors involved. Recently, other categories of abnormal glucose metabolism that are not defined as overt diabetes, such as impaired glucose tolerance (IGT) and impaired fasting glucose (IGF), were introduced. These two conditions also carry a higher risk of future diabetes and probably also of cardiovascular disease [14]. The prevalence of these categories is also increasing and in a recent study the prevalence of IGT in an Australian population was as high as 10.6% [15]. Type 2 diabetes is a descriptive term and a manifestation of a much broader underlying disorder. This includes metabolic syndrome, a cluster of cardiovascular risk factors which apart from glucose intolerance includes hyperinsulinemia, dislipidemia, hypertension, visceral obesity, hypercoagulability and microalbuminuria [16]. This combination of risk factors is partly responsible for the increased risk of cardiovascular disease in diabetes [16].

The prevalence of hypertension is expected to increase in the next 25 years from 26.5% in the year 2000 to 29.2% in the year 2025 [17]. The incidence of hypertension in patients with type 2 diabetes is approximately twofold higher than in age-matched subjects without the disease [18]. The definition of hypertension is different in diabetes, and blood pressure levels above 130/80 mm Hg are already defined as hypertension in diabetic patients [19]. The prevalence of hypertension is particularly high in obese subjects and it increases with age. The pattern of hypertension is changes as patients get older. The systolic blood pressure increases linearly with age across all age ranges, whereas diastolic blood pressure increases with age only until the age of 50 and then levels off and declines. Thus, in the elderly isolated systolic hypertension is more common [20]. Since the prevalence of type 2 diabetes is high in obese subjects and it increases with age, the co-existence of diabetes and hypertension is particularly high in obese and/or elderly patients.

Diabetic patients have more isolated systolic hypertension, and due to autonomic neuropathy they experience less nocturnal fall in blood pressure and higher baseline heart rate than their nondiabetic counterparts [5].

The co-existence of diabetes and hypertension in the same patient is devastating to the cardiovascular system [1, 21] and blood pressure control in these patients is a great challenge, since the target blood pressure is lower and the response to treatment is poor [5].

## Clinical Findings

Diabetes mellitus is associated with a high risk of cardiovascular disease and is the leading cause of end-stage renal disease, blindness, and nontraumatic amputations in western countries [18]. Elevated but nondiabetic levels of fasting glucose also carry a higher risk of cardiovascular disease [14]. As a cardiovascular risk factor, glycemia is a continuous variable with no sudden increase in risk [22]. The extreme state is the metabolic syndrome that is associated with a 2- to 3-fold increase in cardiovascular morbidity and mortality [23–25]. Hypertension by itself is a powerful risk factor for cardiovascular morbidity and mortality.

Although the effects of diabetes mellitus and hypertension on the cardiovascular system vary somewhat and are often distinct, their combined presence in the same patient is destructive [26]. The common denominator of hypertensive/diabetic target organ disease is the vascular tree, which is affected by both disorders.

### *The Vascular Tree*

Both hypertension and diabetes are well-identified risk factors for atherogenesis. Several mechanisms acting together mediate the damage to the vascular tree in the diabetic hypertensive patient [26]. Metabolic abnormalities 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 glycemic 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 [26].

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 2 diabetes and 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 [26]. 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 [26]. 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

Diabetes mellitus is associated with a markedly increased prevalence of coronary artery disease. The prevalence of coronary artery disease as assessed by various diagnostic methods is as high as 55% among adult patients with diabetes mellitus as compared to 2–4% of the general population [27]. Moreover, the cardiovascular mortality rate is more than doubled in men and more than quadrupled in women who have diabetes mellitus compared to those without. The restenosis rate after coronary balloon angioplasty is about 2-fold higher in diabetic than nondiabetic patients [28]. Due to autonomic neuropathy diabetic patients have a decreased perception of ischemic pain, which contributes to a high prevalence of silent ischemia [29]. Diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction [30].

Myocardial ischemia is common in patients with hypertension [31] and caused by several pathogenic mechanisms. (1) Hypertension accelerates arteriosclerosis of the coronary arteries. (2) Elevated blood pressure increases left ventricular wall stress, wall tension, and stroke work. (3) Resistance of the coronary microvasculature is abnormally elevated in hypertensive patients even in the absence of left ventricular hypertrophy. (4) Long-standing hypertension causes left ventricular hypertrophy that increases the diffusion distance, compromises the vasodilator reserve of the coronary circulation and increases the oxygen demand of the myocardium [1, 32]. It should be noted that hypertensive patients, especially those with left ventricular hypertrophy, are as susceptible to silent myocardial ischemia as patients with diabetes [33].

Coronary artery disease is much more common in diabetic hypertensive patients than in patients suffering from hypertension or diabetes alone [34]. For all 2,681 men in the PROCAM trial who had none of the three risk factors (i.e. 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 [34]. Diabetes, and to a lesser extent hypertension, may alter the perception of ischemic pain, leading to a high prevalence of silent ischemia. Melina et al. [35] 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.

### Cardiomyopathy

Several clinical studies have indicated that diabetes mellitus is associated with cardiomyopathy that is independent of atherosclerotic coronary artery disease [36]. Macroscopic changes include muscular hypertrophy with pale appearance and firmness to palpation. Microscopic changes include thickening of the capillary basement membrane, intimal proliferation of small myocardial arterioles and capillary microaneurysms, and focal myocardial fibrosis with an accumulation of interstitial glycoprotein and collagen. Electron microscopy shows perivascular damage with loss of contractile myocardial elements and deposition of either glycoprotein or material that is positive on periodic acid-Schiff stain [1]. Structural changes are associated with impaired ventricular function. Diastolic dysfunction is an early abnormality in diabetic cardiomyopathy and can be diagnosed even in young insulin-dependent diabetic subjects before the onset of systolic dysfunction [37]. Shapiro [38] found abnormal diastolic function in patients with diabetes mellitus who did not have heart disease. Diabetes mellitus seems to have less effect on systolic function [39]. Mustonen et al. [40] found similar resting ejection fraction in diabetic patients and controls. However, during 4 years of follow-up, the left ventricular ejection fraction at rest markedly decreased in diabetic patients only. Several studies have shown that ejection fractions after myocardial infarction are lower in diabetic than in nondiabetic patients [41]. Impaired myocardial systolic and diastolic functions may lead to congestive heart failure. Congestive heart failure is substantially increased in diabetic patients irrespective of coronary artery disease and hypertension [42]. Diabetic patients with coronary artery disease develop more severe congestive heart failure, more hospitalizations and higher risk of mortality than nondiabetic patients [43]. In the SOLVD (Studies of Left Ventricular Dysfunction) trial diabetes was an independent risk factor for morbidity and mortality in heart failure [44]. The negative impact of diabetes on symptoms and prognosis was more pronounced in women [44]. The Framingham study data revealed a fourfold greater incidence of congestive heart failure in diabetic men and an eightfold increase in diabetic women, compared with nondiabetic subjects [45]. In the DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) trial congestive heart failure accounted for up to 66% of mortality during the first year after myocardial infarction in diabetic patients [46]. In a recent study even impaired glucose tolerance, when associated with moderate systolic hypertension, increased the risk of 8-year cardiovascular mortality in men twofold possibly through the presence of the metabolic syndrome [47]. Marroquin et al. [48] followed for 4

years 755 women from the Women's Ischemia Syndrome Evaluation (WISE) study who were referred for coronary angiography to evaluate suspected myocardial ischemia. Compared with women with normal metabolic status, women with the metabolic syndrome had a significantly lower 4-year survival rate (94.3 vs. 97.8%,  $p = 0.03$ ) and event-free survival from major adverse cardiovascular events (death, nonfatal myocardial infarction, stroke, or congestive heart failure; 87.8 vs. 93.5%,  $p = 0.003$ ). The higher risk was evident only in women with angiographically significant coronary artery disease.

Longstanding hypertension leads to left ventricular hypertrophy that may be either concentric or eccentric. Hemodynamic factors explain the increased left ventricular mass; however, clinical blood pressure levels are only weakly related to left ventricular mass [49].

Therefore, nonhemodynamic factors such as sodium intake, activity of growth-promoting hormones (such as insulin and thyroxin), activity of the sympathetic nervous system, rennin-angiotensin system, whole-blood viscosity glucose levels, and genetics probably contribute to the development of left ventricular hypertrophy [1]. Cardiac hypertrophy is not a homogenous process, and growth of nonmyocytic cells, which include endothelial cells, vascular smooth muscle cells, fibroblasts and macrophages participate in the development of left ventricular hypertrophy [50]. In animal models, isoenzymatic changes of cardiac myosin have been described in experimental hypertensive cardiomyopathy [51].

Hypertensive cardiomyopathy is associated with impaired cardiac function [1]. We showed that in hypertensive patients contractility deteriorated as left ventricular mass increased [52]. In early hypertensive heart disease, impaired filling is predominantly caused by decreased ventricular relaxation during early diastole [53]. Patients may have reduced exercise capacity because the stiff left ventricles are unable to accommodate the increased blood volume [54–56]. A progressive decline in ventricular function may lead to congestive heart failure. Data from the Framingham study showed that hypertension was the primary cause of congestive heart failure in 35% of the cases and played a role in this condition in another 40% [57]. In a recent survey conducted in Israel, 75% of patients with congestive heart failure had hypertension and the rate was even higher in those with diastolic dysfunction [58, 59]. The risk to develop congestive heart failure increased by 55% for a 20 mm Hg increase in systolic pressure [60] and was approximately eight times greater when electrocardiographic criteria of left ventricular hypertrophy were present [61].

The coexistence of diabetes and hypertension results in more severe cardiomyopathy than would be expected with either hypertension or diabetes mellitus alone [62]. 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 [1]. Clinical studies with echocardiography also showed an increased left ventricular mass in diabetic hypertensive patients [63, 64]. Grossman et al. [63] 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. Cardiomyopathy of diabetes and hypertension is associated with impaired ventricular function and a high prevalence of congestive heart failure [65].

### *The Kidneys*

The most common causes for end-stage renal disease (ESRD) are diabetes mellitus and hypertension [66]. Patients with diabetes mellitus can develop kidney disease and about one-third develop diabetic nephropathy, which accounts for almost half of all new ESRD cases [66]. Early in the course of diabetic nephropathy, changes in kidney hemodynamics and hyperfiltration lead to an increase in glomerular filtration rate (GFR) [67]. The progression of nephropathy involves characteristic pathologic changes, including accumulation of the extracellular matrix, widening of the glomerular basement membrane, arteriosclerosis, and some degree of interstitial fibrosis [66]. The earliest clinical manifestation of diabetic nephropathy is microalbuminuria (20–200  $\mu\text{g}/\text{min}$ ) which, if left untreated, can progress to overt nephropathy after 10–15 years of diabetes, and is also a marker for cardiovascular disease [68, 69]. In African-Americans, albuminuria may be present in 30–40% of patients with diabetic nephropathy [66].

Hypertension is a well-defined risk factor for ESRD, and accounts for 27% of all ESRD cases in the US and 33.4% of ESRD cases among African-Americans [66]. The risk of ESRD increases as blood pressure increases [70, 71]. Analysis of the data collected from 332,544 men over a 16-year period in the MRFIT study showed that the adjusted relative risk of developing ESRD was 1.9 for high-normal blood pressure, and 22.1 for stage 4 hypertension (according to the JNC 5 criteria), relative to the category of optimal blood pressure [71]. Longstanding hypertension causes arteriolar nephrosclerosis with impaired kidney function. When hypertension is superimposed on diabetes mellitus it accelerates the decrease in renal function. Blood pressure control with levels below 130/80 mm Hg can slow the progression of renal disease in diabetic patients [72].