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Etiology and Prevalence of Hypertension in Diabetic Patients

Data from several epidemiologic studies have suggested that the prevalence of hypertension in patients with diabetes mellitus is ~1.5–2.0 times greater than in an appropriately matched nondiabetic population. In patients with insulin-dependent diabetes mellitus (IDDM), hypertension is generally not present at the time of diagnosis. As renal insufficiency develops, blood pressure rises and may exacerbate the progression to end-stage renal failure. In non-insulin-dependent diabetes mellitus (NIDDM), many patients are hypertensive at the time of diagnosis. The incidence of hypertension in NIDDM is related to the degree of obesity, advanced age, and extensive atherosclerosis that is typically present, and it probably includes many patients with essential hypertension. Several other pathophysiologic mechanisms also contribute to the genesis and maintenance of hypertension in the patient with diabetes. Hyperglycemia and increases in total-body exchangeable sodium may lead to extracellular fluid accumulation and expansion of the plasma volume. In some patients, alterations in the function of the renin-angiotensin-aldosterone system and vascular sensitivity to vasoactive hormones may also play a role. It has recently been suggested that hyperinsulinemia and insulin resistance may also contribute to the maintenance of an elevated blood pressure because insulin is known to promote sodium retention and enhance sympathetic nervous system activity. The evidence for these hypotheses and their respective contributions to the etiology of hypertension in IDDM and NIDDM are discussed. *Diabetes Care* 11:821–27, 1988

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It has been recognized for many years that hypertension and diabetes (or impaired glucose tolerance) coexist more frequently than would be expected by chance alone. However, the pathogenetic relationship between these two common disorders remains elusive. The investigation of the complex interaction between hypertension and diabetes has proceeded along two distinct but interrelated lines. Physicians whose primary area of investigation was hypertension observed a high frequency of diabetes or abnormal glucose tolerance among their hypertensive patients and suggested that hypertension was a prediabetic state (1–3). Conversely, diabetologists focused their attention on the high prevalence of hypertension in their patient populations and its potential adverse effects on the long-term microvascular and macrovascular complications of diabetes (1,4). More recently, these two avenues of investigation have converged in an attempt to identify a unifying pathophysiologic basis for both diseases. In this review, we examine the epidemiologic evidence for the association between diabetes and hypertension and discuss the possible etiologies of abnormal blood pressure regulation in the patient with diabetes mellitus.

EPIDEMIOLOGY AND PREVALENCE

Several studies from the early years of this century suggested that the prevalence of hypertension was increased in patients with diabetes compared with nondiabetic subjects (1–6). In his review of the literature in 1929, Major (1) identified at least 12 reports that addressed this relationship, and he concluded that the most consistent abnormality observed was an elevation of the systolic blood pressure in older diabetic patients. In some series, the prevalence of hypertension was increased as

much as sixfold among diabetic compared with nondiabetic patients (6). In a large series from the Joslin Clinic in 1936, Root and Sharkey (4) reported that ~50% of patients with diabetes have an abnormally elevated blood pressure. However, these older studies suffered from many problems with experimental design or lack of appropriate controls (1–4,6). The confounding effects of obesity (2,3), age (2,3), family history (1–6), and other risk factors for hypertension were frequently not controlled. The diabetic populations often included a mixture of insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetic patients (1–6), and the presence or absence of diabetic nephropathy was often not reported (1–3,5,6). In addition, the criteria for defining hypertension and the methods for obtaining blood pressure determinations were not uniform among the various studies.

Recent epidemiologic studies have more carefully defined the relationship between diabetes and hypertension. In a series of 900 patients with IDDM from the Joslin Clinic, Christlieb et al. (7) noted that the prevalence of hypertension (defined as systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg) was significantly increased compared with controls. It is of interest that the relative risk was greater among female diabetic patients than among their male counterparts. The increased prevalence of hypertension in IDDM may be evident as early as age 13 yr as reported by Moss (8) in a series of 123 diabetic children between ages 8 and 20 yr.

The prevalence of hypertension among patients with NIDDM is frequently more difficult to define. This is partly related to the heterogeneity of NIDDM with respect to its pathogenesis (e.g., obese vs. nonobese) and its treatment (insulin vs. oral agents vs. diet). Nevertheless, certain trends are evident. Pell and D'Alonzo (9) compared 662 diabetic employees of Du Pont with a group of nondiabetic employees who were matched for age, sex, weight, and employment status. They reported a 54% increase in the prevalence of hypertension (defined as a blood pressure >160/95 mmHg) in the diabetic patients. In the Bedford survey, patients with newly diagnosed diabetes as well as those with glucose intolerance were found to have a significantly higher prevalence of systolic hypertension compared with patients with normal glucose tolerance (10). This relationship was present in both men and women after appropriate adjustment for age and weight. In the Whitehall study, patients with impaired glucose tolerance were found to have significant elevations of mean blood pressure, but the results were not significant for patients with overt diabetes (10). In the Framingham study, systolic hypertension was ~1.5 times more prevalent in diabetic than in nondiabetic patients, with the risk being higher in women than in men (11,12). Several other studies, including the population survey conducted in Tecumseh, Michigan (13,14), and a series of elderly diabetic patients (aged 50–79 yr) reported by Barrett-Conner et al. (15), have confirmed that the tendency to develop hypertension is more apparent among diabetic women than diabetic men. Note that all of the aforementioned studies have been conducted in predominantly Caucasian populations residing in industrialized areas of the United States and western Europe. However, data from the World Health Organization's Multinational Study of Vascular Disease in Diabetes has also confirmed an increased prevalence of hypertension among diabetic women (36%) and diabetic men (32%) from diverse ethnic and national origins (16).

Although the results of these (9–16) and other (17,18) surveys may be criticized for the methodologic flaws noted above, some general conclusions may be drawn. First, hypertension is ~1.5–2.0 times more prevalent among patients with NIDDM and/or impaired glucose tolerance than in the normoglycemic population. Although this is frequently attributed to the excessive number of obese and aged patients who comprise the NIDDM population, the trends are also evident in studies in which these variables have been adequately controlled. Second, the hypertension found is frequently characterized by elevations of the systolic rather than diastolic blood pressure, particularly in older diabetic populations. Third, these trends are more evident in women than in men. Finally, the risk for developing hypertension is often seen in patients with impaired glucose tolerance in addition to those with overt diabetes.

NATURAL HISTORY AND COMPLICATIONS

The time course and natural history of hypertension differs markedly in patients with IDDM versus those with NIDDM. In the former, blood pressure is usually normal at presentation and frequently remains normal during the first 5–10 yr of diabetes. Hypertension typically develops in concert with the onset of renal insufficiency and is characterized by elevation of systolic and diastolic blood pressure. In patients who have had IDDM for >30 yr, ~50% will have hypertension (7). This subgroup is almost entirely represented by patients who have developed diabetic nephropathy. Conversely, long-term (>30 yr) survivors of diabetes who have escaped the ravages of diabetic nephropathy are rarely found to have hypertension (7).

In contrast to IDDM, the patient with NIDDM is frequently hypertensive at the time of diagnosis of diabetes. The increase in blood pressure is correlated with the increased prevalence of obesity and the advanced age that is characteristic of the NIDDM population. Approximately 60% of NIDDM patients >60 yr old are hypertensive compared to 25–30% of the nondiabetic population (7). In contrast to IDDM, the natural history of diabetic nephropathy and the contribution of impaired renal function to the development of hypertension in NIDDM is not well defined. Note that isolated systolic hypertension is particularly common in NIDDM and is frequently attributed to the presence of macrovascular disease and the loss of elastic compliance in large arteries (19). In addition, other physical factors

including abnormalities in the microcirculation or altered platelet function may play a role (20,21). It must also be remembered that systolic blood pressure normally rises during the human aging process (22), thus further contributing to the high prevalence of systolic hypertension in NIDDM populations.

In both IDDM and NIDDM the impact of hypertension on excess morbidity and mortality is substantial. It is well known that diabetes is associated with an increased risk of death from renal failure, coronary artery disease, and cerebrovascular disease. When hypertension is superimposed, the risk of death from all causes may increase as much as fourfold (17).

Although end-stage renal disease is the principal cause of death in approximately one-fourth to one-third of patients with IDDM (23–25), the precise relationship between hypertension and the progression to renal failure in patients with diabetes has not been completely defined. Clearly, elevations in blood pressure are frequently seen once end-stage renal disease of any etiology (including diabetic nephropathy) is firmly established. However, recent data suggest that mild or subclinical hypertension may play an important role in accelerating the progression to renal failure in patients with diabetes. Blood pressure is frequently elevated in IDDM patients with proteinuria before the appearance of clinically overt deterioration in renal function (26,27). Even in patients with microalbuminuria, blood pressure is related to the degree of urinary protein excretion (28). Moreover, recent studies have suggested that the predisposition to hypertension, as assessed by family history or an abnormally high rate of erythrocyte sodium-lithium countertransport, may serve as an important marker of those patients who are at increased risk of developing diabetic nephropathy at a time early in the course of IDDM when renal function and blood pressure are still normal (29,30). The importance of these findings is underscored by the fact that antihypertensive therapy has been shown to retard the deterioration in renal function in diabetic nephropathy and may prove to be one of the most important interventions capable of preventing this serious complication (31,32).

The course of other microvascular complications of IDDM, particularly retinopathy, may also be adversely affected by hypertension, although the evidence is less convincing than for diabetic nephropathy. In several studies, the presence of hard exudates, hemorrhages, and proliferative changes have been shown to be significantly correlated with blood pressure (33–35). This association has generally not been observed for the earlier stages of background retinopathy. More important, a causal relationship between hypertension and diabetic retinopathy and the effects of antihypertensive therapy on slowing the progression of retinopathy have not been established.

In NIDDM the principal cause of excess morbidity and mortality is macrovascular disease, including coronary artery, cerebrovascular, and peripheral vascular disease. In the Whitehall study, both systolic and diastolic hypertension conferred a greater risk of mortality from coronary artery disease in diabetic patients than did other major risk factors such as obesity, smoking, and hypercholesterolemia (36,37). In both the Bedford (38) and Whitehall (36,37) studies, the increased risk of coronary heart disease from hypertension was even apparent in patients with impaired glucose tolerance compared to patients with normal glucose tolerance. Several studies have also demonstrated that the risk of stroke and transient ischemic attacks is enhanced in diabetic patients with hypertension compared with normotensive diabetic individuals (39,40). In these studies, as well as in the Framingham study (41), the excess risk from hypertension is generally additive rather than synergistic.

Although the association between hypertension, diabetes, and macrovascular disease is generally well established, there is a paucity of evidence to demonstrate whether blood pressure reduction will improve this excess risk in patients with diabetes. Most large prospective studies that have addressed the effect of antihypertensive therapy on morbidity and mortality (including the Veterans Administration Cooperative Study and the Hypertension Detection and Followup Program; 42–44) have excluded patients with diabetes. Based on our understanding of the pathophysiology of hypertension in nondiabetic individuals, it is not unreasonable to assume that some benefit will also be obtained in patients with diabetes. However, it is clear that more prospective epidemiologic studies on the natural history of hypertension in diabetes, its relationship to metabolic control, and the effects of blood pressure reduction are needed.

ETIOLOGY

In addition to the interactive effects of diabetic nephropathy and macrovascular disease with hypertension, several other factors contribute to the genesis and maintenance of an elevated blood pressure in both IDDM and NIDDM (Table 1). It has traditionally been stated that the hypertension of diabetes is volume dependent, and there are several lines of evidence, both experimental and clinical, that support this notion. First, hyperglycemia increases the osmolality of the extracellular fluid. As water shifts from the intracellular to extracellular space to maintain osmotic equilibrium, the extracellular space is expanded at the expense of intracellular dehydration. Unless hyperglycemia is sufficiently severe to produce an osmotic diuresis, a state of volume overload will exist. Indeed, an increased plasma volume has been demonstrated in both diabetic animals (45) and diabetic humans (46). These data may also explain why institution of appropriate antidiabetic therapy may lead to a reduction in blood pressure. Second, total-body exchangeable sodium is frequently increased in patients with diabetes (47–49), and an exaggerated pressor response to a high-sodium diet has been observed in some diabetic individuals (50). However, the relationship of increased exchangeable sodium to the maintenance of

TABLE 1
Etiology of hypertension in diabetes mellitus

Renal disease
Atherosclerosis
Extracellular volume expansion
Renin-angiotensin-aldosterone system
Altered sensitivity to catecholamines or angiotensin II
Insulin resistance and/or hyperinsulinemia

an elevated blood pressure is unclear because this defect is observed in normotensive as well as hypertensive diabetic patients (47–49). Finally, note that the presence of renal insufficiency in the diabetic patient may impair the ability to excrete water and solutes, thus perpetuating the volume expansion that was induced by hyperglycemia and/or sodium excess.

The contribution of the renin-angiotensin-aldosterone system to the hypertension of diabetes has also been extensively studied. In general, circulating renin levels are low or normal in hypertensive diabetic patients, with the lowest levels being observed in patients with diabetic nephropathy (47,51,52). Although it might be contended that "normal" renin levels are inappropriately elevated for the degree of volume expansion observed in diabetes, it seems clear that absolute overproduction of renin is an uncommon cause of diabetic hypertension. Perhaps the only group of diabetic patients in whom elevated renin levels have been consistently observed are those with dehydration or diabetic ketoacidosis (46). However, this was probably secondary to the severely volume-depleted state that was present.

The etiology of low-renin hypertension in diabetes is thought to arise from several differrent factors. First, the increased extracellular volume (whether arising from the osmotic effects of hyperglycemia, excess sodium retention, or renal insufficiency) would be expected to suppress endogenous renin production. Second, the synthesis and release of renin may be impaired secondary to hyalinization of afferent arterioles or destruction of the juxtaglomerular cells (53,54). Evidence also exists that the cleavage of prorenin to renin may be impaired in diabetes, resulting in excessive release of a biologically less active renin precursor into the systemic circulation (55–57). Finally, it is known that renin release is partially dependent on adrenergic stimulation (58). Thus, in diabetic patients with neuropathy and impaired catecholamine release in response to upright posture or other physiologic stimuli, the stimulation of renin secretion may be defective (45).

Altered vascular sensitivity to pressor hormones may also contribute to the elevated blood pressure observed in patients with diabetes. Weidman et al. (49,59) have demonstrated that the infusion rate of angiotensin II required to produce a 20-mmHg pressor response is significantly lower in diabetic patients than in healthy control subjects, suggesting that vascular responsiveness is enhanced in these patients. However, no significant difference was observed between hypertensive and normotensive diabetic individuals. Because basal plasma renin activity was similar in the diabetic and control patients, the increased sensitivity to angiotensin II may reflect a generalized abnormality in the feedback regulation of the renin-angiotensin-aldosterone system (59). A similar alteration in the vascular responsiveness to norepinephrine infusion has been reported by Weidman et al. (49,59) and others (60), and the abnormal pressor response could be corrected by diuretic therapy (49). Although abnormally high levels of plasma catecholamines may occur in patients with very poor glycemic control (61), circulating levels of norepinephrine and its clearance rate from plasma are generally normal in patients who are metabolically stable without evidence of neuropathy (62,63). Thus, if catecholamines play a significant role in the etiology of hypertension in diabetes, it is more likely via enhanced sensitivity than absolute overproduction.

Recently, a considerable amount of interest has focused on the potential role of insulin in the pathogenesis of hypertension in diabetes. Several lines of evidence have emerged to support this hypothesis. There are a considerable number of epidemiologic studies that have demonstrated that patients with essential hypertension have an increased prevalence of impaired glucose tolerance or overt diabetes compared with normotensive individuals (10,64). The relationship between abnormal glucose tolerance and blood pressure has even been demonstrated within the normotensive population and in children (65,66). In studies from which plasma insulin concentrations are available, the circulating insulin levels are consistently elevated in hypertensive patients after oral glucose ingestion, suggesting the presence of insulin resistance (67–69).

Although one obvious link between insulin resistance, hypertension, and impaired glucose tolerance is their frequent association with obesity, recent data from the Israel Study of Glucose Intolerance, Obesity, and Hypertension suggests that hyperinsulinemia and/or insulin resistance is associated with hypertension even after controlling for the effects of body weight (64). This hypothesis has gained additional support after a recent study with the euglycemic clamp technique demonstrated a moderate to severe degree of insulin resistance in a group of young normal-weight patients with essential hypertension (70).

There are several possible mechanisms through which insulin may mediate an increase in blood pressure. First, the hormone is known to stimulate renal sodium retention, which may predispose to a volume-overloaded state. In healthy humans, insulin infusion stimulates sodium reabsorption by the kidney (71), and similar effects can be demonstrated in vitro (72). Because circulating insulin levels throughout the day are frequently elevated in NIDDM patients due to the presence of insulin resistance, the persistently high levels of insulin may play an important role in initiating and maintaining the increase in total-body sodium. Second, the administration

of insulin with subsequent stimulation of carbohydrate metabolism leads to an activation of the sympathetic nervous system and an increase in circulating norepinephrine levels (73). If sensitivity to catecholamines is enhanced in diabetes, as discussed above, the combined effects of volume expansion and vasoconstriction would be expected to produce a rise in systemic blood pressure. Finally, insulin is known to stimulate the activity of certain membrane ion-transport systems, particularly Na^+-K^+-ATPase and the Na^+-H^+ exchange system (74,75). These effects may change the distribution of ions across vascular smooth muscle (thus altering sensitivity to vasoactive stimuli) or may enhance the reabsorption of sodium or other cations by renal tubular epithelial cells. Although these mechanisms are speculative, they would provide a unifying theory for the common occurrence of insulin resistance, obesity, NIDDM, and hypertension.

Despite the increasing evidence that hyperinsulinemia may play an important role in the genesis and maintenance of hypertension, it is clear that other factors are also operative. More than one-third of NIDDM patients and one-half of IDDM patients remain free of hypertension throughout their lives despite the presence of hyperinsulinemia and insulin resistance. There are several possible mechanisms that might explain this apparent discrepancy. For example, the ability of insulin resistance (or other metabolic derangements that characterize the diabetic state) to cause elevated blood pressures may only occur in patients who also have other genetic risk factors for hypertension, e.g., a positive family history or increased Na^+-Li^+ countertransport. Alternatively, it is possible that some patients have enhanced responsiveness to the ability of insulin to activate sympathetic nervous system activity or promote sodium retention or that they have defects in the production of (or sensitivity to) vasodepressor or natriuretic hormones. These hypotheses are likely to be the subject of intense research efforts in the future.

It is apparent from this brief review that no single hormone or other factor has clearly emerged as the principal pathophysiologic agent to explain the high prevalence of hypertension in diabetes. This no doubt reflects the heterogeneous nature of diabetes itself as well as the lack of understanding of all of the factors that cause hypertension in the nondiabetic population. As knowledge of these mechanisms becomes increasingly clear, more specific and effective therapies may emerge.

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