Predisposition to Essential Hypertension and the Development of Diabetic Nephropathy

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ABSTRACT

Only a subset of insulin-dependent diabetic patients are at risk of developing nephropathy. Prospective studies of uncomplicated insulin-dependent diabetic cohorts have shown that a rise in systemic arterial pressure is a concomitant feature of the progression to early nephropathy. The development of hypertension is an integral feature of established nephropathy in diabetes, and its amelioration retards the progression of disease and may improve overall mortality. Family studies have suggested that nondiabetic parents of insulin-dependent diabetic patients with nephropathy have a greater prevalence of hypertension, and in certain groups of non-insulin dependent patients, it has been found that the blood pressure before the onset of diabetes correlates with the development of nephropathy after the onset of diabetes. These results indicate that a propensity to hypertension may be part of the genetic predisposition to nephropathy. This contention is further supported by the finding that a raised erythrocyte sodium-lithium countercurrent transport, a biochemical marker of hypertension and cardiovascular disease whose activity is largely genetically determined, occurs with greater frequency in proteinuric diabetic patients and their nondiabetic parents than in those diabetic patients without nephropathy and their parents. Recent family studies have also shown that a family history of cardiovascular disease significantly increases the risk of nephropathy by up to three-fold in insulin-dependent diabetes. It is suggested that the cardiorenal complications of diabetes mellitus may be linked to reduced insulin sensitivity, which itself is associated with hypertension, raised sodium-lithium countercurrent transport rates, and cardiovascular disease.

Key Words: hypertension, familial, nephropathy

Nephropathy occurs only in a subset of insulin-dependent diabetic patients, having its highest incidence in the second decade of diabetes (1,2). The clinical syndrome of advanced nephropathy is defined by a total urinary protein excretion rate greater than 500 mg/day, a rapid and relentless decline in renal function, an association with diabetic retinopathy, and almost invariably, systemic arterial hypertension. The main causes of death are related to uremia and cardiovascular disease (3).

Antihypertensive therapy has been shown to retard the rate of progression to end-stage renal failure in insulin-dependent diabetic patients with proteinuria (4). The effect of hypertension in advanced nephropathy has been further underscored by the results of patient survival studies. Earlier reports of cumulative mortality over 10 yr among this group of patients were between 50 and 70% when antihypertensive therapy was not part of routine management (1,2). Parving and Hommel (5) have recently suggested that effective treatment of hypertension in a cohort of proteinuric insulin-dependent diabetic patients over a similar observation period can limit cumulative mortality to 18%. Similarly, Mathiesen et al. (6), comparing two cohorts of insulin-dependent patients with nephropathy routinely managed with or without antihypertensive therapy, reported that the cumulative all-cause mortality after 8 yr was 13% in the group receiving antihypertensive treatment, significantly lower than the 42% rate occurring in the untreated group. The reduction in mortality was due mainly to fewer deaths from uremia, but there are suggestions that cardiovascular mortality may also have decreased in the treated patients.

The association between blood pressure and proteinuria, however, predates the onset of overt clinical nephropathy (7). An increase in systemic blood pressure has been reported by several groups (8–10) in insulin-dependent diabetic patients with microalbuminuria, a stage of incipient nephropathy. Moreover, in prospective studies of microalbuminuric patients, the changes in urinary albumin excretion were paralleled by changes in arterial pressure (11). Both in cross-sectional and longitudinal studies, the associ-
ation between blood pressure and albumin excretion rate was shown to be independent of blood glucose control. In these patients, albumin excretion rate, although higher than normal, is by definition below 200 μg/min and renal function is well preserved, making it unlikely that the increase in blood pressure is a consequence of the renal failure per se. Recent studies of matched normoalbuminuric and microalbuminuric insulin-dependent diabetic patients show that pathologic changes in glomerular structure are more severe in the latter group (12). How these morphologic changes are linked to the development of microalbuminuria and the increase in blood pressure, as well as their relevance to the progression of renal disease, remains, however, to be elucidated. Studies in microalbuminuric patients are unlikely to resolve whether elevations of blood pressure or a predisposition to hypertension makes a contribution to the development of diabetic nephropathy.

The reports of two longitudinal studies have helped in our understanding of the factors that may influence the transition from normoalbuminuria to microalbuminuria. In a study by Mathiesen et al. (13), 209 normoalbuminuric, normotensive, insulin-dependent diabetic patients were monitored for 60 months. Of the 205 patients who completed this study, 7 progressed to persistent microalbuminuria. Initial blood pressure was similar, but the albumin excretion rate was significantly greater and glycosylated hemoglobin was higher in the group of progressors; blood pressure increased in this group only after microalbuminuria had developed for approximately 2 yr. These findings suggested that blood glucose control and the initial level of albumin excretion rate are the main determinants of microalbuminuria and that microalbuminuria precedes and possibly causes the increase in blood pressure. Blood pressure data in this study have to be interpreted with caution in that arterial pressure was only measured yearly to the nearest 5 mm Hg by different observers and the variation in these measurements was significantly greater than that of the albumin excretion rate, which was measured four times a year by a sensitive immunoassay. This lack of precision in blood pressure measurement could have missed changes of between 4 and 5 mm Hg.

In a prospective study by the Microalbuminuric Collaborative Study Group (MCS) (14), the development of persistent microalbuminuria was investigated in 137 normoalbuminuric, normotensive, insulin-dependent diabetic patients who were observed for at least 4 yr. Blood pressure, measured to the nearest 2 mm Hg with a random zero sphygmomanometer, albumin excretion rate, and glycosylated hemoglobin were determined twice yearly. Eleven patients progressed to persistent microalbuminuria and, compared with nonprogressors at baseline, showed a significantly higher mean blood pressure (101 ± 2.4 versus 90 ± 0.9 mm Hg; P < 0.05), albumin excretion rate (14.8 [95% CI, 12.4 to 17.2] versus 4.3 [2.1 to 6.4] μg/min; P < 0.05), and glycosylated hemoglobin (10.4 ± 0.6 versus 8.9 ± 0.2%; P < 0.05). Blood pressure and glycosylated hemoglobin levels remained significantly higher in the group of progressors over the 4-yr observation period. A multiple logistic regression analysis of the data indicated that albumin excretion rate and blood pressure were significant determinants of microalbuminuria. These two studies identify some common determinants of microalbuminuria, namely albumin excretion rate and blood glucose control, but differ in their findings concerning the role of blood pressure. The MCS study clearly indicates that the elevation in blood pressure occurs concomitantly with that of albumin excretion rate and that it does not require the development of microalbuminuria. Indeed, a blood pressure elevation is taking place while albumin excretion is increasing within the normal range in the group of progressors. Although studies in insulin-dependent diabetic patients with a shorter duration of disease will be required to understand the chronologic relationship between the early increases in albumin excretion rate and blood pressure in normoalbuminuric patients progressing to microalbuminuria, some insight into this process comes from a study in Pima Indians developing non-insulin dependent diabetes and proteinuria. In that study (15), systematic measurements of blood pressure were obtained in 356 Pima Indians before the development of diabetes. These were related to the development of proteinuria, measured by albumin/creatinine ratio, after the onset of diabetes. It was found that the incidence of proteinuria was greatest in the patients in the highest third of prediabetic blood pressure (Figure 1), the risk being increased by approximately threefold. All of these studies suggest the premicroalbuminuric evolutionary stages of diabetic nephropathy are associated with an elevation of the systemic arterial pressure. Support for this view is provided by a recent series of family studies of predisposition to hypertension in insulin-dependent diabetic patients with nephropathy.

FAMILY STUDIES

Familial clustering of diabetic nephropathy was first reported by Seaquist et al. (16) and subsequently confirmed by Borch-Johnsen et al. (17), but the factors responsible for this aggregation were not explored in these studies. Higher values of arterial pressure in parents of insulin-dependent diabetic patients with proteinuria were reported by Viberti et al. (18). In that study, blood pressure was directly measured in a standardized manner by a single observer.
In a subsequent study, in which information was collected by means of a questionnaire, Krolewski et al. (19) also reported a significantly higher prevalence of arterial hypertension among the parents of insulin-dependent diabetic patients with microalbuminuria and macroalbuminuria. More recently, in a case-control study, Barzilay et al. (20) showed that patients with advanced nephropathy not only had a greater prevalence of parental hypertension but also higher mean arterial blood pressures during adolescence. Follow-up data in that study showed that the relative risk of developing overt nephropathy was 3.8 if one or more parents were hypertensive. Together, therefore, these studies strongly suggest that a family history of hypertension confers an increased susceptibility to the development of proteinuria in some groups of insulin-dependent diabetic patients. A relationship between parental and offspring blood pressure in insulin-dependent diabetic patients with nephropathy was not found in a study by Jensen et al. (21). The prevalence of hypertension was reported to be 25% in the parents of diabetic patients with nephropathy and 19% in the parents of those without nephropathy. This study analyzed only parents of diabetic patients who had developed nephropathy before the age of 31 yr and did not assess the history of hypertension in the deceased parents. Moreover, although proteinuric patients came from the total clinic population, the selection of the control, uncomplicated group excluded infrequent attenders, a group with presumably poor control but no complications. This could theoretically represent a nonsusceptible-to-complications, low blood pressure group, originating from families with lower blood pressures. These sampling strategies could have led to two results: on the one hand, a reduction of the difference in blood pressure between parents of proteinuric patients and parents of control patients (by exclusion of families with lower blood pressures in this group) and, on the other hand, a comparison of relatively young parental groups in whom differences in arterial pressure may still not have emerged. It is worth noting that in the parents of the diabetic patients with nephropathy, the mean systolic and diastolic blood pressures were 135 and 82 mm Hg, respectively, which are at and less than the 75th and 50th percentiles, respectively, for the age of this group, which averaged 58 yr. These blood pressure values closely correspond to the United Kingdom Office of Population, Censuses and Surveys analysis of blood pressure in a representative group of nonhypertensive subjects between 50 and 64 yr of age in whom the mean values for systolic and diastolic pressures in men were 132 and 82 mm Hg, respectively (22). In this age range, women were reported to have blood pressures similar to those of the men. In the study by Jensen et al., there was a lack of correlation between parental and offspring blood pressures. The correlation coefficient reported \((r = 0.03)\) corresponds to levels usually found between spouses (23). Studies in the general population have reported a significant association between parental and offspring blood pressures (24) and this relationship has been confirmed in diabetic patients (25). In recent years, a greater awareness of the risks of hypertension and the generalized use of antihypertensive drugs may have obscured some of the familial blood pressure associations. It is of interest that a strong relationship between parental and offspring blood pressures was found in the study by Viberti et al. (18), in which blood pressure data were collected between 1953 and 1954, when no routine treatment for hypertension was available.

Recent studies have further defined the familial factors that might be involved in the development of diabetic nephropathy. Insulin-dependent diabetic patients with proteinuria have a significant excess of cardiovascular disease, for which hypertension itself is a major risk factor (3). Whether familial aggregation of cardiovascular disease occurs in diabetic patients with nephropathy was explored in a study of parental cardiovascular morbidity and mortality of two cohorts of insulin-dependent diabetic patients with and without proteinuria (26). The prevalence of cardiovascular disease was found to be significantly greater in the parents of insulin-dependent diabetic patients with nephropathy (31 versus 14%; \(P < 0.01\)), and the frequency of cardiovascular disease as a direct cause of death was also significantly higher (40 versus 22%; \(P < 0.03\)). In this group of parents, the age- and sex-adjusted relative risk for cardiovascular disease was 2.9 (95% confidence interval [CI], 1.5 to 5.5; \(P < 0.001\)). Moreover, a history of cardio-
vascular disease in the father was associated with a significantly increased risk of nephropathy in the diabetic offspring after controlling for age, gender, and duration of diabetes (odds ratio, 3.2; 95% CI, 1.3 to 7.9; \( P < 0.01 \)). Among the diabetic patients with nephropathy, a positive family history of cardiovascular disease was significantly more frequent in those who had suffered a cardiovascular event (odds ratio, 6.2; 95% CI, 2 to 19; \( P < 0.005 \)) (Figure 2). This study, therefore, indicated that a predisposition to cardiovascular disease increases the risk of nephropathy in diabetes and the risk of cardiovascular disease in diabetics with nephropathy and suggested that both disorders may share similar pathogenetic processes, that may have a genetic or shared environmental basis.

**MARKERS OF NEPHROPATHY**

These observations will help in the early identification of insulin-dependent diabetic patients at risk of nephropathy, but their predictive accuracy remains relatively low. Studies of intermediate phenotypes, which are related to the risk of hypertension and cardiovascular disease, may further refine our ability for early detection. A factor that has received much attention in this respect is the red blood cell sodium-lithium countertransport (Na⁺/Li⁺-CT). An elevated activity of this transporter has been found to be consistently associated with essential hypertension (27,28) and some of its renal and cardiovascular complications (29-31). In insulin-dependent diabetes, increased Na⁺/Li⁺-CT rates have been found in patients with both microalbuminuria and macroalbuminuria (19,21,32,33). Parents of proteinuric insulin-dependent diabetic patients with high Na⁺/Li⁺-CT have also been found to have elevated values in one study (34), although not in another (21), confirming the high heritability of the rates of Na⁺/Li⁺-CT described in the general population and in subjects with arterial hypertension (35,36). In further support of this view is a recent report of a close correlation between Na⁺/Li⁺-CT rates in identical twins discordant for diabetes (37). In a study of 185 consecutive insulin-dependent diabetic patients (38), the prevalence of elevated Na⁺/Li⁺-CT activity (i.e., >0.41 mmol/L red blood cells per hour) was found to be 21.5, 42.8, and 51.7% in normoalbuminuric, microalbuminuric, and proteinuric patients, respectively—a highly significant difference (\( P < 0.005 \)) by analysis of variance. The percentage of patients with proteinuria (microalbuminuria and macroalbuminuria) significantly increased with increasing quartiles of the Na⁺/Li⁺-CT distribution (Figure 3). Na⁺/Li⁺-CT activity significantly correlated with albumin excretion rate (\( r = 0.38; \( P < 0.001 \)) and mean arterial pressure (\( r = 0.37; \( P < 0.001 \)), and an increased activity conferred a fourfold risk of developing proteinuria. In a multiple logistic regression analysis, Na⁺/Li⁺-CT emerged as the most important determinant of proteinuria, followed by duration of diabetes, mean blood pressure, and glycosylated hemoglobin (Table 1). Of interest, the prevalence of supranormal Na⁺/Li⁺-CT decreased consistently with the duration of diabetes in normalalbuminuric patients, reaching a low of 15% for those patients with more than 20 yr of diabetes, a group at low risk of nephropathy. An interaction was observed between Na⁺/Li⁺-CT and blood glucose control as determinants of proteinuria in that the highest frequency occurred in those patients with glycosylated hemoglobin values above the median and Na⁺/Li⁺-CT rates above the normal range. These findings are in accord with those reported by Krolewski et al. (19), who showed that the risk of renal disease was increased by eightfold in those diabetic patients with elevated Na⁺/Li⁺-CT rates and an index of hyperglycemia above the median. Na⁺/Li⁺-CT activity has also been shown to be associated with lipid abnormalities in diabetic patients with albumin excretion rates spanning the normal to microalbuminuric range (33). That lipid abnormalities occur in microalbuminuric patients before any loss of renal function has been reported.
by several authors (39,40). This link between Na+/Li+-CT (a risk factor for hypertension) and lipid abnormalities and poor blood glucose control (both risk factors for macrovascular and microvascular disease) may find an explanation in an altered insulin sensitivity in these patients.

Lopes de Faria et al. (41) studied two groups of normotensive, nonproteuric, insulin-dependent diabetic patients with normal and elevated Na+/Li+-CT. Using a hyperinsulinemic euglycemic clamp technique, these authors demonstrated greater resistance to peripheral insulin action in the group with high Na+/Li+-CT and found a significant association between reduced insulin sensitivity and increased serum triglycerides, apolipoprotein B, and left ventricular hypertrophy. That study was the first to give insights into a possible metabolic basis for the association of an altered cell membrane ion transport system predictive of cardiovascular risk and other risk factors for vascular complications. Interestingly, preliminary reports in non-insulin dependent diabetes indicate that insulin resistance is associated with microalbuminuria (L. Groop et al., personal communication), a strong predictor of cardiovascular disease mortality in that group of patients (42–44). A growing body of evidence supports the role of insulin resistance per se as a significant risk factor for cardiovascular disease (45).

The activity of Na+/Li+-CT is under important genetic control (35,36), and it is possible that the processes with which this ion transport system is associated also recognize a similar genetic influence. Further studies are required to clarify these aspects. Not all cases of insulin-dependent diabetic patients developing nephropathy generate from families positive for hypertension or develop hypertension themselves. Approximately 15% of these proteinuric patients remain normotensive, and interestingly, they show a significantly lower rate of decline in GFR and have Na+/Li+-CT rates within the normal range (46). These findings suggest a less severe course of nephropathy in a subset of patients but also highlight the multifactorial nature of this complication of diabetes.

**CONCLUSIONS**

Hypertension is an integral feature of the clinical manifestation of diabetic renal disease, and its amelioration in proteuric insulin-dependent diabetic patients retards the rate of loss of renal function and appears to reduce overall mortality. In microalbuminuric diabetic patients, too, antihypertensive therapy lowers albumin excretion rate and has been claimed to prevent overt nephropathy (47,48). Prospective studies in normoalbuminuric insulin-dependent diabetic patients have shown that an elevation in arterial pressure occurs concomitantly with an increase in albumin excretion rate in those patients progressing to microalbuminuria. This temporal relationship suggests not only that renal disease per se is unlikely to be responsible for the initial increase in blood pressure, but also that an initial elevation in blood pressure may contribute to the development of nephropathy.

Longitudinal studies have now indicated that in non-insulin dependent diabetic patients, prediabetic raised blood pressure levels are associated with a significantly increased risk of developing protein-
This tendency to an elevation in systemic arterial pressure has been shown to have a familial basis in that an excess of parental hypertension is found in proteinuric diabetic patients. A positive family history of cardiovascular disease has also been found to increase the risk of developing nephropathy in diabetes. The view of a genetic susceptibility to nephropathy and its cardiovascular complications is further strengthened by evidence that diabetic nephropathy itself clusters in families and that a biochemical marker of essential hypertension and cardiovascular disease such as Na⁺/Li⁺-CT, which is under strong genetic control, is abnormal in proteinuric insulin-dependent diabetic patients and their parents. An increased Na⁺/Li⁺-CT activity in insulin-dependent diabetic patients confers a fourfold risk of developing nephropathy and is associated with poor glycemic control, lipid disturbances, left ventricular hypertrophy, and reduced insulin sensitivity. An aggregation of risk factors for cardiorenal complications with a strong familial (genetic) basis thus seems to occur in a subset of diabetic patients.

REFERENCES


14. Messent J on behalf of the Microalbuminuria Collaborative Study Group: Arterial blood pressure and glycaemia in the progression from normoalbuminuria to persistent microalbuminuria in type 1 (insulin-dependent) diabetes mellitus—the 4 year follow up findings. Diabetes 1991;40(suppl 1):A1228.

15. Knoller WG, Bennett PH, Nelson RG: Prediabetic blood pressure predicts albuminuria after development of NIDDM. Diabetes 1988;37(suppl);120A.


26. Earle R, Walker JD, Hill C, Viberti GC: Familial...


