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Familial, hemodynamic and metabolic factors in the predisposition to diabetic kidney disease

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Familial, hemodynamic and metabolic factors in the predisposition to diabetic kidney disease. Proteinuric diabetic patients have an increased risk of cardiovascular disease and almost always have hypertension. In the early stages of diabetic renal disease (microalbuminuria) when renal function is well preserved, systemic arterial blood pressure is already elevated compared to insulin-dependent diabetic patients without microalbuminuria. Prospective studies have shown that normoalbuminuric patients who progress to microalbuminuria have higher blood pressures (albeit within the normal range) than those who persistently remain normoalbuminuric. Parents of insulin-dependent diabetic patients with nephropathy have a higher prevalence of hypertension and cardiovascular disease compared to those of patients without nephropathy. Moreover, diabetic nephropathy clusters within families. Erythrocyte sodium-lithium countertransport activity, the most consistent marker for essential hypertension and its cardiorenal complications, is elevated in diabetic patients with nephropathy and in their non-diabetic parents. These data suggest that a familial predisposition to arterial hypertension and cardiovascular disease increases the risk for the development of nephropathy and its associated cardiovascular complications in insulin-dependent diabetes. Arterial hypertension is a state of insulin resistance and diabetic patients susceptible to nephropathy have been found to be less insulin sensitive. Preventive strategies of diabetic kidney disease in the future will have to take into account its metabolic hemodynamic and familial basis.

Nephropathy occurs only in a subset of approximately 30% of insulin-dependent diabetic patients, having its highest incidence in the second decade of diabetes [1, 2]. In non-insulin-dependent diabetes the cumulative incidence of proteinuria after 20 years of the disease varies between 25% in Caucasian populations to approximately 50% in other ethnic groups.

Proteinuria

Persistent clinical proteinuria is closely associated with the presence of hypertension in IDDM patients [1]. In NIDDM patients the risk of developing clinical proteinuria is increased more than twofold in patients with blood pressure >165/95 mm Hg compared to those with lower blood pressure after adjusting for age, sex and duration of diabetes [3]. Moreover, in both insulin-dependent and non-insulin-dependent diabetes, the age adjusted total mortality rate is greatly increased in those patients with proteinuria or hypertension [4, 5].

In insulin-dependent diabetes the development of clinical proteinuria occurs through a continuous progressive rise of albumin excretion rate (AER) from the normal (AER <30 mg/24 hr) and across the microalbuminuric range (AER 30 to 300 mg/24 hr). Once clinical proteinuria is established, renal function declines in a relentless fashion and systemic arterial blood pressure rises concomitantly [6]. However, prior to the development of clinical proteinuria systolic and diastolic blood pressure levels are already significantly elevated in patients with microalbuminuria compared to those of patients with normoalbuminuria [7, 8]. In this spectrum of AER, changes in AER over time have been shown to be significantly positively correlated with changes in mean blood pressure [8].

Renal function is well preserved at the stage of microalbuminuria and therefore, renal failure is unlikely to be the cause of the observed rise in systemic blood pressure. In comparative studies of matched insulin-dependent diabetic patients with or without microalbuminuria, the presence of microalbuminuria has been shown to be associated not only with a rise in systemic blood pressure but also with poorer blood glucose control [9], lipid abnormalities [10, 11], and more severe pathological changes within the kidney [12]. Long-term longitudinal studies have shown that microalbuminuria is the strongest independent predictor of the development of clinical nephropathy in insulin-dependent diabetes [13, 14] and of early mortality and cardiovascular disease in non-insulin dependent diabetes [15]. A recent prospective study in non-insulin-dependent diabetic patients demonstrated that 80% of the total mortality in the microalbuminuric group was due to cardiovascular causes [5].

Transition to microalbuminuria

Studies in normoalbuminuric patients may assist us in understanding the factors which determine in a subset of patients the transition from normal albumin excretion rate to microalbuminuria. Two longitudinal studies have explored this issue. Mathiesen et al [16] followed up 205 normoalbuminuric, normotensive insulin-dependent diabetic patients for 60 months. Seven progressed to persistent microalbuminuria. Compared to patients who did not progress and remained normoalbuminuric, initial AER was significantly greater and glycosylated hemoglobin higher in the group of progressors. However, baseline blood pressure was similar and rose in the progressors only after microalbuminuria (defined as AER > 20 μg/min) had developed for approximately two years. 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 rise in

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Table 1. Predictors of development of microalbuminuria in IDDM patients

Variables	β coefficients	P value
AER	4.10	0.012
MBP	0.23	0.003
Smoking	2.13	0.049

blood pressure. Blood pressure data in this study have to be interpreted with caution in that arterial pressure was only measured once a year to the nearest 5 mm Hg by different observers, and the variation in these measurements was significantly greater than that of the AER 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) [17], the factors affecting the development of persistent microalbuminuria was investigated in 137 non-microalbuminuric non-hypertensive insulin-dependent diabetic patients, who were observed for at least four years. Eleven patients progressed to persistent microalbuminuria and compared to non-progressors showed at baseline a significantly higher mean ± SD mean blood pressure 101 ± 2.4 versus 90 ± 0.9 mm Hg ($P < 0.05$), geometric mean (95% CI) albumin excretion rate 14.8 (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 four-year observation period. Moreover, the patients who progressed to microalbuminuria had a significantly greater percentage of smokers. The cumulative incidence of microalbuminuria was 8%. A stepwise logistic regression analysis indicated that initial albumin excretion rate, blood pressure and smoking were significant determinants of microalbuminuria (Table 1). Glycosylated hemoglobin just missed conventional significance ($P < 0.06$) and was excluded from the regression model.

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 rise in blood pressure occurs concomitantly to that of albumin excretion rate and that it does not require the development of microalbuminuria. Indeed, a blood pressure rise is taking place while albumin excretion is increasing within the normal range in the group of progressors. Studies in insulin-dependent diabetic patients with shorter duration of disease will be required to understand the chronological relationship between the early increases in albumin excretion rate and blood pressure in normoalbuminuric patients progressing to microalbuminuria.

Two recent studies in NIDDM patients underscore the primary importance of early elevations in blood pressure. In a study in Pima Indians [18], systematic measurements of blood pressure were obtained in 356 subjects before the development of diabetes. Arterial pressure values were then related to the development of proteinuria measured as albumin/creatinine ratio, after the onset of diabetes. It was found that the incidence of proteinuria was threefold higher in the patients in the highest tertile of prediabetic blood pressure. A five-year prospective study of 39 Japanese patients with NIDDM and normoalbuminuria demonstrated that age-adjusted mean arterial pressure (98.2 ± 3.4 vs. 87.3 ± 2.4; $P < 0.05$) and frequency of hypertension (72.7% vs. 17.4%; $P < 0.01$) were significantly greater initially in the 11 patients who developed microalbuminuria compared to the 23 patients who remained normoalbuminuric [19]. All these findings taken together strongly support the view that pre-microalbuminuric evolutionary stages of diabetic nephropathy are associated with an elevation of the systemic arterial pressure. This early rise in systemic blood pressure suggests that a predisposition to hypertension may be an important feature in the genesis of nephropathy.

Familial factors

Evidence for genetic determinants in the development of nephropathy has come from several sources. Familial clustering of diabetic nephropathy was first reported by Seaquist et al [20] and subsequently was confirmed by other workers [21]. The factors responsible for this aggregation were, however, not explored in these studies. Higher values of arterial pressure in parents of insulin-dependent diabetic patients with proteinuria than in parents of matched IDDM patients with normoalbuminuria were reported by Viberti et al [22] in a study in which blood pressure was directly measured in a standardized manner. This observation was confirmed by Krolewski et al [23] who, using information collected by means of a questionnaire, reported a significantly higher prevalence of arterial hypertension among the parents of insulin-dependent diabetic patients with micro- and macroalbuminuria. These studies, though not confirmed by all authors [24], suggest that a family history of hypertension confers an increased susceptibility to the development of proteinuria in subgroups of insulin-dependent diabetic patients. Further definition of the familial factors involved in the development of diabetic nephropathy has come from the observation that parents of insulin-dependent diabetic patients with proteinuria have a significant excess of cardiovascular disease compared to parents of insulin-dependent diabetic patients who did not develop kidney disease. Earle et al [25] found that the prevalence of cardiovascular disease was significantly greater (31% vs. 14%; $P < 0.01$) and the frequency of cardiovascular disease as a direct cause of death was also significantly higher (40% vs. 22%; $P < 0.03$) in the parents of insulin-dependent diabetic patients with nephropathy. In this group of parents, the age- and sex-adjusted relative risk for cardiovascular disease was 2.9; 95% CI 1.5 to 5.5 ($P < 0.001$). A history of cardiovascular disease in both parents or in the father alone was associated with an age, sex and duration of diabetes adjusted increased risk of nephropathy in the diabetic offspring of approximately 10- and threefold, respectively (Fig. 1). 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; $P < 0.005$). This study indicated that in insulin-dependent diabetes, a predisposition to cardiovascular disease increases the risk of nephropathy and the risk of cardiovascular disease in those with nephropathy, and suggested that both disorders may share similar pathogenetic processes which may have a genetic or shared environmental basis.

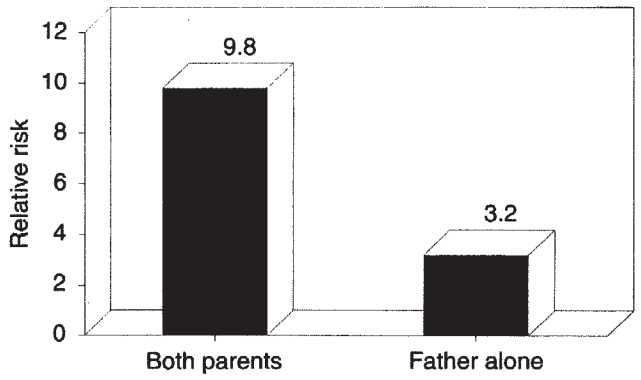

Fig. 1. *Relationship of family history of cardiovascular disease and relative risk of nephropathy in IDDM offspring.*

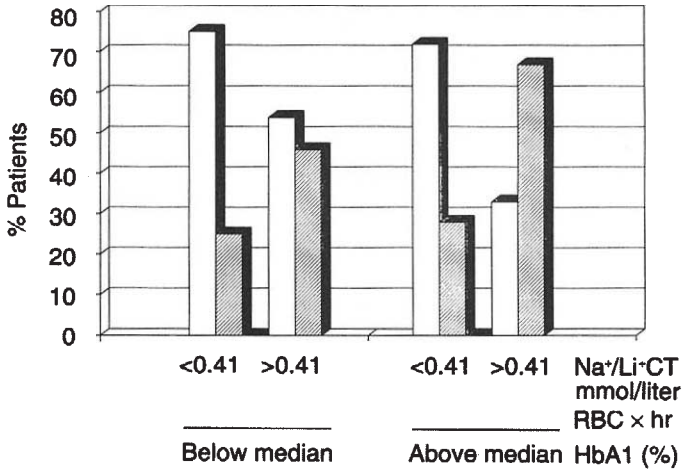

Fig. 2. *Relationship of the frequency of IDDM patients with nephropathy (hatched bars) and without nephropathy (open bars) above and below the upper limit of normal of sodium-lithium countertransport activity (0.41 mmol/liter rbc × hr) according to the distribution of glycosylated hemoglobin (HbA_1).*

Sodium-lithium countertransport and insulin sensitivity

An elevated erythrocyte sodium-lithium countertransport activity (Na^+/Li^+-CT) is the most consistent marker for essential hypertension [26] and its interindividual variability is largely under genetic control [27, 28]. Furthermore, raised Na^+/Li^+-CT has been found to be associated with some of the renal and cardiovascular complications of arterial hypertension [29–31]. In insulin-dependent diabetes, raised Na^+/Li^+-CT rates have been found in patients with both micro- and macroalbuminuria by several [32, 33] though not all authors [34]. Parents of proteinuric insulin-dependent diabetic patients with high Na^+/Li^+-CT have also been found to have elevated values in one study [35], though not in another [24], confirming the high heritability of the rates of Na^+/Li^+-CT described in the general population and in subjects with arterial hypertension [36].

In a study of 185 consecutive insulin-dependent diabetic patients [37] the prevalence of supranormal Na^+/Li^+-CT activity (that is, >0.40 mmol/liter RBC × hr) was found to be 21.5, 42.8 and 51.7 percent in normoalbuminuric, microalbuminuric and proteinuric patients, respectively, a highly significant difference ($P < 0.005$ by ANOVA). The percentage of patients with proteinuria (micro- and macroalbuminuria) significantly increased with increasing quartiles of the Na^+/Li^+-CT distribution. Sodium-lithium countertransport activity significantly correlated with albumin excretion rate ($r = 0.38$, $P < 0.001$) and mean arterial pressure ($r = 0.37$, $P < 0.001$), and a raised 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. The frequency of patients with proteinuria was greatly increased in the category of patients with Na^+/Li^+-CT above the upper limit of normal who also had glycosylated hemoglobin values above the median (Fig. 2). This link between Na^+/Li^+-CT on the one hand, and higher arterial pressure and worse blood glucose control, both risk factors for macro- and microvascular disease, on the other, may find an explanation in an altered sensitivity to insulin. Lopes de Faria et al [38] studied two groups of normotensive, non-proteinuric 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. This study which has recently been confirmed [39] 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. Hyperinsulinemia and insulin resistance have been implicated in the risk of cardiovascular disease in the general population [40]. Strategies for the prevention of diabetic kidney disease must in the future take in consideration the hemodynamic, metabolic and familial bases of this complication of diabetes mellitus.

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