Renal Hemodynamics and Albumin Excretion Rate in Patients With Diabetes Secondary to Acquired Pancreatic Disease

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OBJECTIVE — To assess kidney function and AER in patients with PD.

RESEARCH DESIGN AND METHODS — Thirty-three patients with PD (age 52 ± 7 yr, duration of disease 11 ± 6 yr, BMI 24 ± 3 kg/m^2) and 33 patients with IDDM were matched for sex, BMI, and duration of disease. GFR and RPF were determined by single injection of [^{51}Cr]EDTA and [^{125}I]hippurate. AER was measured by radioimmunoassay in a single timed overnight urine collection.

RESULTS — GFR and RPF were, respectively, 113 ± 35 and 441 ± 145 ml · min^{-1} · 1.73 m^2 in patients with PD and 123 ± 30 and 549 ± 94 ($P < 0.001$) in IDDM. FF was significantly higher in patients with PD (0.26 ± 0.05 vs. 0.22 ± 0.03; $P < 0.001$). Prevalence of hyperfiltration (GFR >135 ml · min^{-1} · 1.73 m^2) was similar in both groups (30% in patients with PD vs. 28% in those with IDDM). Geometric mean of urinary AER was 10.4 μg/min (range 1–186) in patients with PD and 11.2 (1–198) in IDDM patients. Some 30.3% of patients with PD and 18% of those with IDDM were microalbuminuric (AER >20 μg/min). By multiple regression analysis, AER was significantly related to systolic ($P < 0.04$) and diastolic blood pressure ($P < 0.01$) and to BMI ($P < 0.03$) in patients with PD. Retinopathy was more frequent in microalbuminuric patients with PD than in those without elevated AER.

CONCLUSIONS — We suggest that early renal abnormalities occur similarly in patients with PD and IDDM.

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AER, ALBUMIN EXCRETION RATE; PD, PANCREATIC DISEASE; BMI, BODY MASS INDEX; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; GFR, GLOMERULAR FILTRATION RATE; RPF, RENAL PLASMA FLOW; FF, FILTRATION FRACTION.

The pathogenesis of diabetic microangiopathy is still unclear. It is controversial whether the metabolic abnormalities related to the duration of diabetic disease are the major determinants of microvascular diabetic complications (1). Some studies have addressed the possibility of genetic predisposition, in addition to the altered diabetic milieu, for the development of diabetic complications (2,3).

Vascular lesions, similar to those of spontaneously diabetic animal models, occur in animals made diabetic with streptozocin, alloxan, or by pancreatic resection (4). In humans, a diabetic condition may be caused by acquired pancreatic diseases, such as pancreatitis, hemochromatosis, tumors, and partial and total pancreatectomy (5). Distinct features of diabetes mellitus secondary to pancreatopathy are impaired insulin secretion, increased insulin sensitivity, reduced ketogenesis, and blunted glucagon response (5,6).

It has been claimed that diabetic complications, such as retinopathy and nephropathy, rarely occur in secondary diabetes (7). Several reasons can explain this possible lower prevalence of diabetic complications. First, secondary diabetes is often of short duration because until recently, the survival rate of patients with chronic PD has been low (8). Second, their lower serum cholesterol and poor nutritional intake with concomitant hepatic disease may confer a protective effect on microangiopathy to these patients (5).

However, in the last two decades, more accurate epidemiological studies have shown that vascular complications do occur in patients with secondary diabetes. We have reported that 31% of 54 patients with diabetes secondary to pancreatopathy had background retinopathy (9). Similar results were presented by Couet et al. (10). In both studies, the degree of retinopathy was less severe than in IDDM. Little information is available on the histology of renal damage in

pancreatic diabetes (11,12). Only two studies have addressed the occurrence of microalbuminuria (a predictor of clinical nephropathy both in IDDM and NIDDM) in diabetes secondary to pancreatopathy (13,14). Even less information is available with respect to renal function in these patients.

The aim of this study was to evaluate if early renal abnormalities of IDDM (hyperfiltration and microalbuminuria) also occur in patients with diabetes secondary to acquired pancreatic disease. Renal hemodynamics and AER were, therefore, determined in a group on insulin-treated patients with secondary diabetes and compared with those of matched IDDM patients.

RESEARCH DESIGN AND METHODS

— Forty-two patients with diabetes secondary to chronic pancreatitis who were <65 yr old and were attending the Metabolic Unit of Treviso Hospital (Veneto, Italy) between 1985 and 1989 were identified. Only 34 met the inclusion criteria for the study—i.e., they were euglycemic when the diagnosis of chronic pancreatitis was made, and they were treated by insulin at the time of the study. One patient declined to participate in the study. Hyperglycemia was subsequent to the onset of PD in all patients, and diagnosis of diabetes was made at least 2 yr after that of pancreatitis. The diagnosis of chronic pancreatitis was defined by the following criteria: *1*) a positive history of recurrent pancreatitis with biochemical evidence of organ damage, and 2) pancreatic calcifications on the abdominal X ray or at ultrasonography. Seven patients were taking ranitidine (150 mg/day) because of the presence of duodenal ulcer. All 33 patients were taking pancreatic enzyme preparations and insulin. No patient presented with severe steatorrhea. Although 30 patients were considered to have alcoholism at the time of diagnosis of PD, no one was taking more than 50 g of alcohol/day at the time of this study. Only 10% of the patients showed a slight increase in transaminase levels without any other sign of liver failure, and no one had liver cirrhosis. Twelve patients (36%) had a positive family history for diabetes.

Table 1—*Clinical features of patients with diabetes secondary to acquired PD and IDDM patients*

	PD PATIENTS WITH SECONDARY DIABETES	IDDM PATIENTS
N	33	33
AGE (YR)	52 ± 7*	44 ± 8
DURATION OF DIABETES (YR)	11 ± 6	11 ± 6
BMI (KG/M^2)	24 ± 3	24 ± 4
C-PEPTIDE (NG/ML)	0.75 (0.2--2.1)*	0.18 (0.1–0.42)

Values are means ± SE or means (ranges) except *n*.
*$P < 0.05$.

Thirty-three IDDM patients were selected by one of the authors (R.N.) from the registry of Internal Medicine of the University of Padua to match individually sex, duration of diabetes, and BMI of the patients with diabetes secondary to PD. All these patients were regularly attending the outpatient clinic for many years, and they were characterized by low or normal body weight, severe hyperglycemia, ketosis, and an immediate need for insulin therapy. All patients had a very low, if detectable, plasma C-peptide level in the fasting state and a C-peptide value <1 ng/ml after i.v. glucagon injection. Table 1 gives clinical features of the two groups.

Patients were admitted to the metabolic ward at 0700; all food, coffee, alcohol, and tobacco had been prohibited from 2200 of the previous night. Each patient was instructed in the collection of a timed overnight urine collection to be completed on the morning of the study. Volume was measured to the nearest 2 ml, and an aliquot was taken for measurement of AER. A fresh midstream specimen of urine was collected for culture to exclude the presence of infection. After at least 10 min rest in the supine position, arterial blood pressure (phases I and V) in the right arm was measured to the nearest 2 mmHg with a standard mercury sphygmomanometer. The morning dose of insulin was withheld until after the observations were complete. A blood sample was taken without cuffing for metabolite and hormone determinations. An i.v. infusion of insulin was then started. Blood glucose was monitored at regular intervals and the insulin infusion rate adjusted to maintain blood glucose concentrations between 4 and 6.5 mM throughout the study protocol. The fundus oculi of each patient was examined by the same ophthalmologist, who was unaware of the cause of each patient's diabetes.

GFR and RPF were measured by monitoring the clearance of [^{51}Cr]EDTA and [^{125}I]hippurate (both given in a single bolus injection), and were corrected to 1.73 m^2 surface area (15). In our unit, GFR of healthy controls ranges from 90 to 135 ml · min^{-1} · 1.73 m^2.

All subjects gave their informed consent to the study, which was approved by the Ethical Committee of the University of Padua and performed according to the Declaration of Helsinki.

Urinary albumin concentration was determined by radioimmunoassay (16). AERs were expressed as μg/min, and microalbuminuria was defined by overnight AER between 20 and 200 μg/min. Plasma glucose was assayed by glucose oxidase method (Glucose Analyzer, Beckman, Fullerton, CA). HbA_{1c} was determined by microcolumn chromatography (Bio-Rad Lab, Richmond, CA). Plasma C-peptide and glucagon were measured by radioimmunoassay technique (9). Concentrations of cholesterol and triglycerides were measured by enzymatic colorimetric techniques (17,18).

Statistics

Data are expressed as means ± SD, unless otherwise stated. Comparisons between groups were tested for significance using the two-tailed Student's *t* test for unpaired samples. The χ^2 test was used

to test for the significance of differences between frequencies. Spearman's test was used to determine the correlation of two variables. Multivariate analysis was used to estimate the independent associations of a number of variables. Log transformation was applied to AER because of its positively skewed distribution. The level of statistical significance was 0.05.

RESULTS — No significant difference was found between patients with secondary diabetes and IDDM patients in glycemic control (glycemia, 8.9 ± 1.9 vs. 9.2 ± 2.3 mM; HbA_{1c}, 7.5 ± 1.2 vs. 8.0 ± 1.4%), daily insulin dose (35 ± 18 vs. 38 ± 15 U/day), total cholesterol (5.4 ± 1.2 vs. 5.5 ± 1.2 mM), triglycerides (1.4 ± 0.8 vs. 1.5 ± 0.9 mM), creatinine (84 ± 19 vs. 83 ± 15 μM), urea (5.52 ± 1.3 vs. 5.32 ± 1.4 mM), and plasma glucagon concentration (120 ± 78 vs. 110 ± 40 pg/ml). Residual insulin secretion, as indicated by fasting C-peptide plasma concentrations, was significantly higher in patients with diabetes secondary to pancreatopathy than in type I diabetic patients (Table 1). The prevalence of retinopathy was similar in both groups: 9 patients with secondary diabetes had background retinopathy (27.3%) vs. 11 IDDM patients (33.3%) (NS). One IDDM patient had proliferative retinopathy.

Urinary AER ranged from 1 to 186 μg/min, with a geometric mean of 10.4 μg/min in patients with diabetes secondary to pancreatopathy, and from 1 to 198 μg/min with a geometric mean of 11.2 μg/min in IDDM patients (Fig. 1). No patient had overt proteinuria. The prevalence of microalbuminuria was higher in patients with secondary diabetes (30.3%) than in IDDM patients (18%), even though the difference was not statistically significant.

Systolic and diastolic blood pressure were comparable between patients with diabetes secondary to pancreatopathy (126 ± 28 and 83 ± 9 mmHg) and type I diabetic patients (125 ± 26 and 80 ± 6, respectively). The prevalence of hypertension (defined as blood pressure values >140/90 mmHg) was higher in patients with secondary diabetes (8 patients, 24%) than in type I diabetic patients (5 patients, 15%), but this difference was not statistically significant.

GFR, RPF, and FF are shown in Table 2. All patients were studied after at least 2 h of euglycemia to prevent the confounding effect of different glucose levels on renal hemodynamics. The mean GFR in patients with secondary diabetes was not significantly different from that of type I diabetic patients (Fig. 2). The prevalence of hyperfiltration (defined as a GFR >135 ml · min^{-1} · 1.73 m^2) was similar in the two groups (30.3% in patients with secondary diabetes vs. 28%, NS).

RPF was significantly lower in patients with secondary diabetes (441 ± 145 vs. 549 ± 94 ml · min^{-1} · 1.73 m^2, $P < 0.001$). As a consequence, FF was higher in this group of patients (Table 2).

In patients with diabetes secondary to pancreatopathy, AER was significantly correlated with systolic blood pressure ($r = 0.345$; $P < 0.05$) and diastolic blood pressure ($r = 0.351$; $P < 0.05$). A similar relationship was also present in type I diabetic patients (AER vs. systolic blood pressure: $r = 0.385$; $P < 0.05$; AER vs. diastolic blood pressure: $r = 0.348$; $P < 0.05$). In patients with diabetes secondary to pancreatopathy, no significant associations were present between AER and age (r =

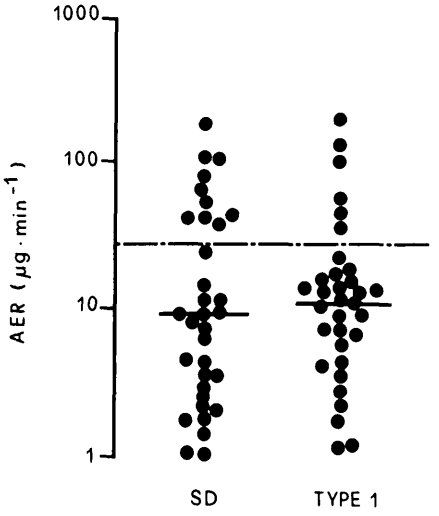

Figure 1—*Urinary AER in 33 patients with diabetes secondary to pancreatopathy (SD) and 33 IDDM patients (TYPE 1). Dotted line indicates the upper limit of normal. Solid horizontal bars indicate geometric means.*

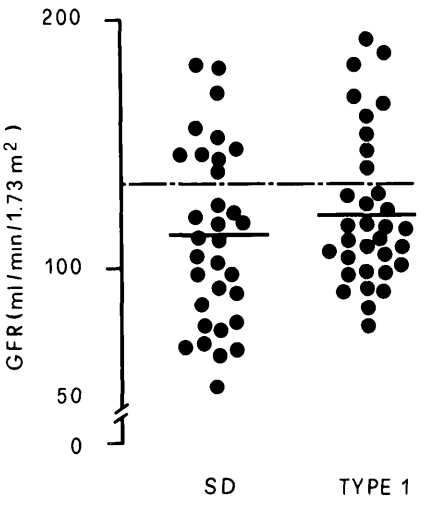

Figure 2—*GFR in 33 patients with diabetes secondary to pancreatopathy (SD) and 33 IDDM patients (TYPE 1). Dotted line indicates the upper limit of normal. Solid horizontal bars indicate mean values.*

Table 2—***Renal hemodynamics in patients with diabetes secondary to acquired PD and IDDM patients***

	PD PATIENTS WITH SECONDARY DIABETES	IDDM PATIENTS
GFR (ML · MIN^{-1} · 1.73 M^2)	113 ± 35	123 ± 30
RPF (ML · MIN^{-1} · 1.73 M^2)	441 ± 145	549 ± 94*
FF	0.26 ± 0.05	0.22 ± 0.03*

Values are means ± SE.
*$P < 0.001$.

Table 3—*Clinical features and renal function in patients with diabetes secondary to pancreatopathy with and without microalbuminuria*

	WITH MICROALBUMINURIA	WITHOUT MICROALBUMINURIA
N	10	23
AGE (YR)	50 ± 8	53 ± 7
DURATION OF DIABETES (YR)	11 ± 5	10 ± 6
BMI (KG/M^2)	25.7 ± 3*	22.1 ± 2
C-PEPTIDE (NG/ML)	0.74 ± 0.72	0.76 ± 0.81
HbA_{1c} (%)	7.08 ± 0.95	7.83 ± 1.27
BLOOD PRESSURE (MMHG)		
SYSTOLIC	136 ± 11*	126 ± 12
DIASTOLIC	89 ± 9*	78 ± 6
CREATININE (μM)	84 ± 19	84 ± 19
GFR (ML · MIN^{-1} · 1.73 M^2)	102 ± 34	118 ± 34
RPF (ML · MIN^{-1} · 1.73 M^2)	409 ± 129	456 ± 149
FF	0.25 ± 0.04	0.27 ± 0.05
RETINOPATHY (%)	50*	17

Values are means ± SE, except where noted.
*$P < 0.05$.

−0.217), duration of diabetes (r = 0.216), GFR (r = 0.102), RPF (r = −0.087), creatinine (r = 0.037), HbA_{1c} (r = −0.027), and fasting glucose levels (r = 0.011).

GFR was significantly related to HbA_{1c} (r = 0.341; $P < 0.05$) and to RPF (r = 0.854; $P < 0.01$) in patients with diabetes secondary to pancreatopathy. Linear regression analyses did not reveal significant relationships for either GFR and RPF with BMI, blood pressure, AER or fasting levels of plasma glucose, C-peptide, and glucagon.

To explore further the features associated with microalbuminuria in patients with secondary diabetes, we compared clinical data and renal function of these patients with and without microalbuminuria (Table 3). Blood pressure values and BMI were significantly greater in microalbuminuric patients. The prevalence of retinopathy was significantly higher in patients with microalbuminuria.

In all patients with diabetes secondary to pancreatic disease, a multivariate regression analysis was performed to evaluate the significant determinants of AER (dependent variable). Blood pressure levels (systolic blood pressure, t value = 2.3115, $P < 0.04$; diastolic blood pressure, t = 2.3217, $P < 0.01$) and BMI (t = 2.4003, $P < 0.03$) were the only significant independent determinants of AER. Other parameters taken into the regression were: HbA_{1c}, age, duration of diabetes, GFR, RPF, C-peptide, and glucagon plasma concentrations.

In Table 4, we compared the clinical features and renal function of patients with diabetes secondary to pancreatopathy with and without a positive family history of diabetes. Only FF was significantly higher in patients with a family history of diabetes. The prevalence of microalbuminuria (33% in patients with family history vs. 29% in those without) and of hyperfiltration (33% vs. 29%) was similar in both groups.

CONCLUSIONS— This study shows that the prevalence of hyperfiltration and microalbuminuria in patients with diabetes secondary to acquired pancreatic disease is similar to that of IDDM patients. We suggest that these abnormalities represent an early stage of diabetic nephropathy in patients with secondary diabetes. It remains to be established whether overt nephropathy will develop subsequently in these patients.

In IDDM, microalbuminuria has been demonstrated to be a good predictor for the subsequent development of clinical diabetic nephropathy, conferring a 20-fold higher risk of progression to overt renal disease in comparison with normoalbuminuric patients (16,19). Microalbuminuria also is an independent risk factor for cardiovascular mortality in NIDDM patients (20,21), in IDDM patients (22), and in the general population (23).

HLA antigens (in particular the phenotipic prevalence of B_8, DR3, DR4, and DR3-DR4) in a group of insulin-requiring patients with diabetes secondary to pancreatopathy attending the same Metabolic Unit, studied some years ago (13), were similar to those found in the

Table 4—*Clinical features and renal function in patients with diabetes secondary to pancreatopathy with and without a family history of diabetes*

	FAMILY HISTORY OF DIABETES	
	WITH	WITHOUT
N	12	21
AGE (YR)	51 ± 7	52 ± 8
DURATION OF DIABETES (YR)	14 ± 6	10 ± 6
BMI (KG/M^2)	24.3 ± 3	24.3 ± 3
C-PEPTIDE (NG/ML)	0.94 ± 1.03	0.64 ± 0.55
HbA_{1c} (%)	7.5 ± 1.3	7.5 ± 1.2
BLOOD PRESSURE (MM HG)		
SYSTOLIC	128 ± 20	131 ± 14
DIASTOLIC	82 ± 10	85 ± 7
GFR (ML · MIN^{-1} · 1.73 M^2)	111 ± 40	114 ± 32
RPF (ML · MIN^{-1} · 1.73 M^2)	401 ± 122	460 ± 151
FF	0.34 ± 0.11	0.25 ± 0.04*
AER (μG/MIN)†	15 (2–100)	8 (1–186)
RETINOPATHY (N)	1	8

Values are means ± SE, except where noted.
*$P < 0.005$.
†Geometric mean (range).

normal nondiabetic population. Therefore, our results suggest that those genetic factors associated with the susceptibility to IDDM are not necessary for the development of renal abnormalities. The different age between the two groups of patients cannot affect our results. No significant correlation was present in both groups of patients between age and AER or kidney function. Duration of diabetes, rather than age, is believed to play a role in the pathogenesis of diabetic complications (1).

This study confirms our previous report on a high prevalence of abnormal AER in patients with hyperglycemia secondary to pancreatic diabetes. At variance with type I diabetes, microalbuminuria also was found in three pancreatopathic patients with a short duration of diabetes. It cannot be excluded, in this case, that an elevated AER reflects a renal damage secondary to pancreatopathy rather than a consequence of diabetic state. Larsen et al. (14) reported a lower prevalence of microalbuminuria (4%) in patients with secondary diabetes. This discrepancy may be attributable at least in part, to the exclusion of patients with arterial hypertension. Although a substantial number of patients with essential hypertension have microalbuminuria (24), it is unlikely that the high prevalence of microalbuminuria could account for our inclusion of patients with hypertension. Blood pressure values were only marginally elevated in our patients with secondary diabetes. In essential hypertension, elevated urinary albumin excretion may result from systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg (24). However, this does not exclude the possibility that even milder degrees of hypertension could contribute to the manifestation of renal abnormalities in hyperglycemic patients. Although the difference did not reach statistical significance, the prevalence of hypertension (defined as blood pressure levels >140/90 mmHg) was higher in patients with secondary diabetes than in type I diabetic patients.

Glomerular hyperfiltration is found in ~20–40% of type I diabetic patients (25). Elevated GFR has been implicated in the initiation and progression of renal disease. There is convincing evidence in animal models that hemodynamic factors, in particular intraglomerular pressure, play an important role in the development of glomerulopathy (26). However, the prognostic significance of glomerular hyperfiltration remains controversial in humans. Two ongoing prospective studies of different design, a case control and a cohort study, have failed to resolve the controversy after 8 yr of observation (27,28). No information is available regarding kidney hemodynamics in patients with secondary diabetes. This study demonstrates that, in secondary diabetes, hyperfiltration has a prevalence similar to that of IDDM. The significant positive relationship between GFR and HbA_{1c} suggests that chronic hyperglycemia can play a role in determining this hemodynamic abnormality, as it has been demonstrated in IDDM patients (29). No relationship was found between GFR and glucagon levels or duration of diabetes.

An interesting finding is the significantly lower RPF and higher FF in patients with secondary diabetes when compared with IDDM patients. The mechanisms responsible for this hemodynamic abnormality are not clear. Increased renal vasoconstriction may reduce RPF if blood pressure and cardiac output remain normal. The combination of reduced RPF with increased FF might suggest an increase in resistance in renal efferent arterioles, with a subsequent increased intraglomerular pressure. Such abnormalities have been described in patients with essential hypertension (30). These changes in renal hemodynamics have been implicated in the pathogenesis of microalbuminuria. In our patients, however, there was not a significant relationship between these parameters and AER. This does not rule out the possibility that these abnormalities, already present before the appearance of microalbuminuria, could explain, at least in part, the high prevalence of microalbuminuria in patients with secondary diabetes.

Also note the finding of a positive association between microalbuminuria and arterial pressure in patients with secondary diabetes. In IDDM, there is a consistent association of microalbuminuria with higher levels of blood pressure, which is independent of age, sex, duration of diabetes, and blood glucose control (31). On the other hand, AER did not exhibit a significant relationship with either plasma glucose, HbA_{1c} levels, or with kidney hemodynamics in patients with secondary diabetes. Only long-term prospective studies will help to better clarify the time course of renal function and AER in these patients. However, the association of blood pressure with AER in patients with secondary diabetes raises the possibility that elevated blood pressure levels may be one of the factors contributing to renal damage or, alternatively, that high blood pressure and increased AER may represent different manifestations of a common process responsible for the development of diabetic nephropathy.

Our study revealed an association between microalbuminuria and retinopathy in diabetes secondary to pancreatopathy, in agreement with previous observations in IDDM and NIDDM patients (32,33). Less clear is the meaning of the significant positive association of AER with BMI in our patients with secondary diabetes. Although proteinuria has been found in obese patients (34), none of our patients was obese.

In patients with secondary diabetes, a family history of diabetes mellitus was present in 36%, which is similar to the rates reported by others (10). It has been suggested that a family history of diabetes was related to an increased prevalence of retinopathy in secondary diabetic patients (10,35). However, no difference in the prevalence of microalbuminuria and hyperfiltration was observed in our patients with and without a

family history of diabetes, confirming our previous study about the prevalence of retinopathy in these group of patients (9).

These data clearly suggest that the early renal abnormalities observed in IDDM also can occur in diabetes secondary to acquired PD. However, no overt nephropathy was observed in these patients. Several factors—such as late onset of diabetes, relatively short duration, better metabolic control, and nutritional deficits—can explain the absence of severe renal complications.

Although this study did not show a significant relationship between metabolic control and AER, we suggest that chronic hyperglycemia secondary to pancreatopathy may play a permissive role for the development of renal abnormalities similar to those described in IDDM patients. Recent studies conducted among IDDM patients indicate the existence of a genetic susceptibility to diabetic nephropathy, but this liability seems independent from that predisposing to diabetes itself (3,36). Therefore, it cannot be excluded that similar genetic factors, possibly related to essential hypertension, could also contribute to the development of diabetic nephropathy in other hyperglycemic conditions.

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