The Prevalence and Severity of Microvascular Complications in Pancreatic Diabetes and IDDM

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OBJECTIVE — To investigate and compare the prevalence, associations, and severity of retinopathy and nephropathy in patients with pancreatic diabetes (PD) and insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS — Thirty patients with PD due to alcohol-induced chronic pancreatitis were matched for age, sex, and duration of diabetes with 30 patients with IDDM. Retinopathy was assessed by fluorescein angiography using the Wisconsin classification. Renal function was assessed by albumin excretion rates (AERs) in at least two timed overnight urine collections and glomerular filtration rates (GFRs) by single injection of ^{51}Cr-EDTA. Microalbuminuria was defined as AER 20–200 μg/min and nephropathy as AER >200 μg/min.

RESULTS — Retinopathy was found in 33% of patients with PD and in 40% with IDDM. The spectrum of disease was similar in the two groups. The geometric mean of AER was 15 μg/min (range 1–1,541) in the PD group and 24 μg/min (2–2,288) in the IDDM group. Nephropathy was found in 7 PD and in 5 IDDM patients, and a reduced GFR was present in 8 (26%) and 4 (13%) of the two groups, respectively. Microalbuminuria occurred in 9 (33%) and hyperfiltration in 3 (10%) in each group. These differences were insignificant. Retinopathy correlated with AER in both groups. Retinopathy and AER correlated with duration of diabetes in the IDDM but not in the PD group.

CONCLUSIONS — Microvascular complications are equally common and severe in PD and IDDM, and improved glycemic control should be the goal in both.

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AER, albumin excretion rate; GFR, glomerular filtration rates; IDDM, insulin-dependent diabetes mellitus; PD, pancreatic diabetes.

Until recently, there was a perception that microvascular complications, particularly retinopathy, were rare in patients with diabetes secondary to chronic pancreatitis (1–3). During the past few years, however, a similar prevalence of retinopathy, albeit less severe (4,5), and of microalbuminuria and glomerular hyperfiltration have been described in pancreatic diabetes (PD) and insulin-dependent diabetes mellitus (IDDM) patients (6). These similarities may support a common pathogenesis for microvascular complications in diabetes of differing etiology. This study evaluates the prevalence, association, and severity of both retinopathy and nephropathy in matched cohorts of patients with PD and IDDM. Retinopathy was assessed by fluorescein angiography, and nephropathy by estimation of multiple overnight albumin excretion rates (AERs) and glomerular filtration rates (GFRs).

RESEARCH DESIGN AND METHODS

Patients

The study participants regularly attended either the Gastro-intestinal or Diabetic Clinic of Groote Schuur Hospital. Thirty Gastro-intestinal Clinic patients with diabetes secondary to alcohol-induced chronic pancreatitis were matched for age, sex, and duration of diabetes with 30 IDDM patients attending the Diabetic Clinic. The investigator matching the patients was blinded to all clinical information other than the factors used for matching. Alcoholism was defined as an alcohol intake of >100 g/day of many years' duration. The diagnosis of chronic pancreatitis was made on the basis of pancreatic calcification on abdominal X ray (26 patients) and at least moderate changes of chronic pancreatitis on endoscopic retrograde cholangiopancreatography (4 patients) as defined by Kasugai et al. (7). The clinical characteristics of the two groups, which were composed of 24 subjects of mixed ancestry, 5 Caucasian,

TABLE 1—*Clinical and biochemical characteristics of the patients studied*

	IDDM patients	PD patients
n (M/F)	30 (28/2)	30 (28/2)
Age (years)	47.2 ± 1.9	48.0 ± 1.9
Duration of diabetes (years)	7.5 (1–35)	8 (1–33)
Body mass index (kg/m^2)	25.9 ± 1.0	20.8 ± 0.7
Insulin dose (U/day)	42.1 ± 2.7	38.5 ± 4.4
HbA_1 (%)	10.0 (6.3–15.7)	10.4 (6.2–23.4)
Cholesterol (mmol/l)	5.7 ± 0.2	5.0 ± 0.3
Systolic blood pressure (mmHg)	131 ± 3	130 ± 3
Diastolic blood pressure (mmHg)	83 ± 2	81 ± 2
History of hypertension (*n*)	8	3
Smokers (*n*)	19	25
Family history of diabetes (*n*)	10	7
History of pancreatitis (years)	—	17.8 ± 1.7
History of calcification (years)	—	8.4 ± 1.5
History of steatorrhea (years)	—	7.6 ± 1.3

Data are *n*, means ± SE, or mean (range).

and 1 African (PD group) and 24 subjects of mixed ancestry, 5 African and 1 Caucasian (IDDM group) are given in Table 1. No significant differences were noted.

All subjects gave written informed consent for this study, which was approved by the University of Cape Town Research and Ethics Committee.

General methods

Records of previous hospital visits were scrutinized. Subjects underwent routine clinical examination, and serum creatinine, cholesterol, and HbA_1 were measured. The designated blood pressure was taken as the mean of clinic blood pressure recordings over the previous 3 years. Urinary albumin concentrations were determined turbidimetrically using a Technicon kit (Bayer Diagnostics, Mulgrave, Australia). HbA_1 was measured using ion-exchange columns (Boehringer Mannheim, Indianapolis, IN). The normal range was 5–8%.

Retinopathy

A single ophthalmologist, unaware of the etiology of the diabetes, evaluated the retinas of all patients using fluorescein angiography. Retinopathy was graded using the Wisconsin classification (8).

Nephropathy

Microalbumin estimation. Three consecutive 12-h overnight urine samples were collected, and the mean of a minimum of two microalbumin concentrations in adequate collections was calculated. Subjects were free of symptoms of urinary tract infection at the time, and urine cultures were negative. Normal microalbumin excretion was defined as <20 μg/min, microalbuminuria 20–200 μg/min, and overt albuminuria as >200 μg/min.

GFR. ^{51}Cr-EDTA GFR values were measured using a standard technique (9) and corrected to a surface area of 1.73 m^2. A GFR that fell outside of the mean ± 2 SDs for the age was regarded as abnormal (10).

Statistical analysis

The data are expressed as means ± SE unless otherwise stated. The range and medians were used for the microalbumin concentrations, GFR values, and duration of diabetes, because of their wide variance. Comparisons between groups were tested for significance using analysis of variance, Wilcoxon's signed rank, and χ^2 tests where appropriate. The correlations between retinopathy and other variables and between AER (log-transformed) and other variables were determined by Spearman's rank correlation and Pearson's test, respectively. $P < 0.05$ was accepted as significant.

RESULTS

Retinopathy

The prevalence and overall spectrum of retinopathy was similar in the two groups (Table 2). Retinopathy only correlated with duration of diabetes ($r = 0.4875$, $P = 0.009$) in the IDDM group; there was no correlation with the HbA_1 concentration or family history of diabetes in either group. Of the subjects with retinopathy, abnormal AERs were found in 67% of those with IDDM and in 60% of those with PD.

Nephropathy

The prevalence of microalbuminuria, glomerular hyperfiltration, reduced GFR, and overt nephropathy was similar in the two groups (Fig. 1 and Table 2). AER correlated positively with retinopathy and negatively with GFR in the PD ($r = 0.6385$, $P = 0.0001$; $r = -0.3937$, $P = 0.0318$) and IDDM ($r = 0.4963$, $P = 0.0053$; $r = -0.4846$, $P = 0.0066$) groups, respectively. The correlation between AER and duration of diabetes was significant in the IDDM group ($r = 0.3667$, $P = 0.046$). There was no correlation between AER and HbA_1 or systolic or diastolic blood pressures in either group. The mean blood pressures in the IDDM and PD groups with overt nephropathy were higher, albeit insignificantly, than in those with no evidence of nephropathy (IDDM: 132 ± 5/82 ± 3 vs. 126 ± 4/83 ± 2 mmHg, PD: 135 ± 5/84 ± 3 vs. 127 ± 4/80 ± 3 mmHg).

CONCLUSIONS — The frequency of retinopathy and nephropathy, as well as their correlation with each other, was similar in these well-matched groups of patients with IDDM and PD. These findings, supportive of other recent reports (4–6), contradict the early perception

Table 2—*Renal and retinopathy data in the patients with IDDM and PD*

	IDDM patients	PD patients
Retinopathy	12 (40)	10 (33.3)
Background		
Minimal (2A)	5 (17)	5 (17)
Mild (2B)	6 (20)	1 (3)
Moderate (2C)	0	2 (7)
Severe (2D)	0	2 (7)
Proliferative (3)	1 (3)	0
AER (μg/min)	15 (1–1,541)	27 (2–2,288)
Microalbuminuria	9 (33)	9 (33)
Nephropathy	5 (17)	7 (23)
GFR (ml/m^2)	98 (6–148)	89 (20–142)
Hyperfiltration	3 (10)	3 (10)
Normal GFR	23 (77)	19 (63)
Reduced GFR	4 (13)	8 (27)
Serum creatinine (mmol/l)	90 (65–501)	89 (50–233)

Data are *n* (%) or mean (range). $P > 0.05$ for all.

that microvascular complications seldom occurred in PD (1–3). It is possible that this perception was due to reduced life expectancy in patients with alcohol-induced pancreatitis.

The severity of the microvascular complications demonstrated in this study was unusual in comparison with previous reported series of patients with diabetes secondary to alcoholic pancreatitis or pancreatectomy (1–6). In those studies only early background retinopathy, glomerular hyperfiltration, and microalbuminuria were found. Our findings are in keeping with the observations by Mohan et al. (11), who reported that 3 of their 40 patients (8%) with diabetes secondary to tropical pancreatitis had proliferative retinopathy. Additionally, in another report, 7% had overt nephropathy (urinary protein excretion >500 μg), and 17% renal insufficiency (serum creatinine >133 μmol/l) (12). The typical clinical diagnosis of diabetic nephropathy was not confirmed histologically in these studies, but autopsy findings of diabetic glomerulosclerosis have been described in isolated cases of PD (13). These data suggest that all forms of renal dysfunction and retinopathy may occur in PD. The reason for the discrepancy in the severity of the microvascular complications in these studies is unclear. A possible explanation may be relatively poor glycemic control in the early stages of the disease in the patients with tropical diabetes and those in our study.

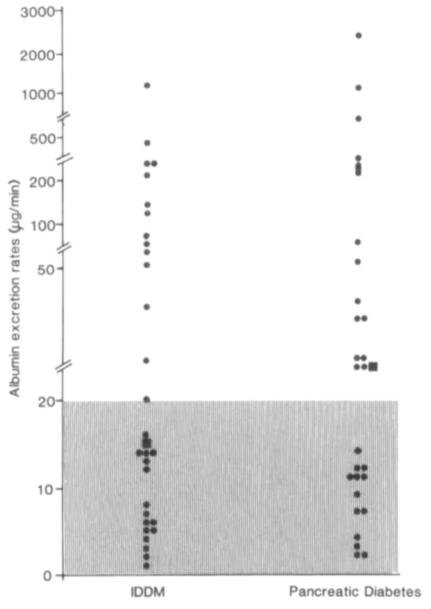

Figure 1—*AERs in the IDDM and PD groups. The ■ indicates the median in each group. The hatched area indicates the normal range.*

There was no association in the present study or in other studies between recent glycemic control and retinopathy or AER in either group (4,5,11,14–17). These findings contrast with the strong association between long-term glycemic control and the presence and severity of retinopathy and microalbuminuria in IDDM (8,14,15). The importance of glycemic control is further emphasized by the findings of the Diabetes Control and Complications Trial in which improved glycemic control significantly diminished the risk of the development of retinopathy as well as its progression (18). In light of this, the relationship appears to be between long-term, not short-term, glycemic control and these complications.

Like Tiengo et al. (6), we found no association between AER and duration of diabetes in the patients with PD, but contrary to previous reports, there was no association between retinopathy and duration of diabetes in the PD group of the present study (4–6,11,17). The reason for the latter is unclear but may relate to the small sample size or to relative inaccuracy in determination of the onset of diabetes. The lack of association between microalbuminuria and blood pressure in both the PD and IDDM groups, irrespective of the presence or absence of a history of hypertension in this study, conflicts with the findings of Tiengo et al. (6). The relationship between arterial blood pressure and microalbuminuria remains controversial (16,19).

Diabetic control in patients with PD is often less than meticulous because of their increased liability for alcohol-induced hypoglycemia, and the tendency in some centers has been to undertreat rather than overtreat such patients (20). In view of the beneficial effect of tight glycemic control on the microvascular complications in IDDM and presumably in other forms of diabetes, this issue warrants review. Improved glycemic control should be sought after careful consideration of additional factors such as continued excessive alcohol ingestion, poor nutrition, and possible impaired counter-

regulatory hormone responses to hypoglycemia.

In summary, we have demonstrated that microvascular complications correlate with each other and occur with similar frequency and severity in well-matched groups of PD and IDDM patients. The similarity in the microvascular complication profile despite differences in pathogenesis of the underlying disease may suggest a common pathogenetic mechanism.

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