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LK, FLUORESCEIN LEAKAGE; D, CAPILLARY DILATATION; LS, CAPILLARY LOSS.

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Effect of Pancreatic Elastase on Diabetic Nephropathy

Pathological change of diabetic nephropathy is characterized by a thickening of the glomerular basement membrane. Although blood glucose and BP are important factors in the control of diabetic nephropathy, the two factors alone may be insufficient in slowing the course of the disease (1). Elastase is a pancreatic enzyme that hydrolyzes elastin and regulates the metabolism of elastin in arterial walls and connective tissues (2). Pancreatic elastase showed an inhibitory effect on the thickening of the glomerular basement membrane in experimental diabetic animals (3). We studied the inhibitory effect of pancreatic elastase on nephropathy in diabetic patients whose blood glucose and BP remained stable.

Thirty-six (14 men and 22 women) nonobese NIDDM patients with >10 yr diabetes duration were studied. Of the patients, 50% were maintained on diet and sulfonylurea and 50% on diet and insulin. All patients had diabetic retinopathy and showed >100 mg/g creatinine of the urinary albumin index from >7 mo before the study. Hypertension was found in 27 of 36 patients and was normalized or corrected by administration of anti-hypertensive drugs, whose doses and sorts were not changed in >3 yr. We gave the patients either 10,800 U of pancreatic elastase (Eisai, Tokyo, Japan) b.i.t. (group 1, $n = 23$) or 300 mg of dilazep dihydrochloride (group 2, $n = 13$), a drug known as an antiplatelet agent, three times a day for 12 mo. The data were analyzed by Duncan's multiple range test. Data were shown as means ± SE.

BMI, FBG, HbA_{1c}, sBP, dBP, and total cholesterol levels remained constant in both groups during the study. In group 1, the albumin index dropped significantly after 2 mo and remained at this level for up to 12 mo. No significant changes were seen in albumin index with group 2. Serum levels of creatinine and urinary levels of NAG (NAG-I) and β_2MG (β_2MG-I) did not change in either group (Table 1). No abnormalities were noted in general laboratory findings, including hematology and chemistry, during the study.

Table 1—*Clinical characteristics of study subjects before and after administration of pancreatic elastase (group 1) or dilazep dihydrochloride (group 2)*

	Group 1		Group 2	
	Before	12 mo after	Before	12 mo after
Age (yr)	63.1 ± 1.7	64.1 ± 1.7	63.8 ± 2.6	64.8 ± 2.6
BMI (kg/m^2)	22.4 ± 0.4	22.5 ± 0.4	22.1 ± 0.4	22.2 ± 0.5
FBG (mM)	6.8 ± 0.2	7.0 ± 0.2	6.5 ± 0.2	6.6 ± 0.3
HbA_{1c} (%)	8.0 ± 0.1	8.0 ± 0.2	7.7 ± 0.1	8.1 ± 0.2
sBP (mmHg)	145 ± 2	139 ± 4	145 ± 2	142 ± 2
dBP (mmHg)	81 ± 2	79 ± 3	82 ± 2	80 ± 3
Total cholesterol (mM)	5.4 ± 0.1	5.1 ± 0.1	5.2 ± 0.1	5.2 ± 0.2
Creatinine (μM)	79.9 ± 3.4	84.8 ± 3.5	78.9 ± 4.8	83.1 ± 6.2
Albumin index (mg/g creatinine)	509.5 ± 82.8	281.7 ± 64.6*	524.7 ± 100.8	429.8 ± 118.2
NAG-I (U/g creatinine)	18.0 ± 1.5	17.9 ± 2.1	19.1 ± 2.1	18.2 ± 2.8
β_2MG-I (μg creatinine)	1235.3 ± 345.1	1055.9 ± 301.7	1237.4 ± 382.8	1049.4 ± 303.9

Data are means ± SE.
*$P < 0.01$.

A significant inhibitory effect of pancreatic elastase on increased albuminuria in diabetic patients was discovered. During the course of the study, body weight, blood glucose, HbA_{1c}, and BP levels remained unchanged. The decreased albuminuria, therefore, was not the result of changes in these factors. However, pancreatic elastase did not affect urinary levels of either NAG or β_2MG, reflecting renal tubular function. This result may indicate pancreatic elastase does not act on the tubular basement membrane, but mainly on the glomerular basement membrane.

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BP, BLOOD PRESSURE; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; BMI, BODY MASS INDEX; FBG, FASTING BLOOD GLUCOSE; sBP, SYSTOLIC BLOOD PRESSURE; dBP, DIASTOLIC BLOOD PRESSURE.

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Glucotoxicity and oxidative hemolysis in G-6-PD deficiency

Hemolysis in a G-6-PD–deficient subject may occur as a result of drug administration (1), infection (2), renal failure (3), insulin (4), diabetic ketoacidosis (5), and hypoglycemia (6). We report a 30-yr-old insulin-requiring diabetic individual who developed the complication in the absence of these conditions.

P.S., a 30-yr-old surgeon presented with polyuria, polydipsia, and a weight loss of 10 kg over the preceeding 3 mo. His appetite was normal, he had no major illnesses in the past, and he was not known to be G-6-PD deficient. He had no family history of diabetes mellitus. He was not on any medication.

On examination, he was 173 cm tall and weighed 61 kg (BMI 20 kg/m^2). His pulse was 90 bpm and BP was 120/80 mmHg. He had no pallor, jaundice, cyanosis, clubbing, or peripheral lymphadenopathy. On examination, cardiovascular, respiratory, alimentary, and neurological systems were normal.

The investigations were as follows: Hb 15.8 g/dl; WBC 8250 cells/mm^3; (P:42, L:56, E:2); erythrocyte sedimentation rate 2 mm/1st h; FPG 14.99 mM; postglucose plasma glucose 1 h :25.7 mM, 2 h :22.15 mM; serum insulin 0 h 27.6 pM; 1-h postglucose 60 pM; 2-h postglucose 21.6 pM; HbA_1 16.5%; cholesterol 4.34 mM; triglycerides 1.02 mM; blood urea 9.3 mM; serum creatinine 97.24 μM. Urinalysis revealed glycosuria. The chest (pa) X ray and electrocardiogram were normal.

The patient was treated with a meal plan of 1650 kcal/day (carbohydrate 55%, protein 20%, fat 25%) and a split dose insulin regimen (regular 12 and Lente 16 before breakfast and regular 8 and Lente 12 before dinner).

The patient presented with jaundice 3 days later. On examination he was pale and had icterus, however, the vital functions and systemic examination were normal. The Hb was 7.0 g/dl, WBC count was 6700 cells/mm^3, and the reticulocyte count was 14.4%. The G-6-PD activity was deficient. The serum bilirubin was 3.8 mg/dl; direct bilirubin 0.6 mg/dl; indirect bilirubin 3.2 mg/dl, serum glutamate pyruvate transaminase 71 U/L; serum alkaline phosphatase 50 U/L; blood glucose 10.06 mM; serum creatinine 97.24 μM; urinalysis revealed glycosuria. The Hb electrophoresis revealed an HbA fraction. Serum electrolytes were normal. The anti-nuclear antibody and the anti-DNA antibody were absent.

The patient was diagnosed with hemolysis in erythrocytes deficient in G-6-PD. The patient was managed conservatively on diet, intravenous fluids, and regular insulin. Hb gradually rose to 11.6 g/dl on 5/3/91, and the patient was discharged on a meal plan of 1700 kcal/day and a split-dose insulin regimen.

The patient as of today (9/28/92) has gained 7 kg and is well controlled on the prescribed regimen. He has had no further episodes of hemolysis.

Hemolysis in G-6-PD–deficient subjects is the result of oxidative damage to erythrocytes (7). Oxidative stress is observed in subjects with chronic hyperglycemia because of enhanced production of oxygen free radicals (8,9). These, in turn, produce cellular injury (10). Hyperglycemia appears to be the operative mechanism in precipitating hemolysis as other factors (1–6) were excluded.

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G-6-PD, GLUCOSE-6-PHOSPHATE DEHYDROGENASE; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; BMI, BODY MASS INDEX; BPM, BEATS PER MINUTE; BP, BLOOD PRESSURE; WBC, WHITE BLOOD CELLS; FPG, FASTING PLASMA GLUCOSE.

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