Decrease in Mortality From Diabetic Nephropathy in Pima Indians

Between 1975 and 1989, the death rate from diabetic nephropathy in the Pima Indians of the Gila River Indian Community declined by 44%, and we proposed that this decline could have resulted from greater access to and improvements in renal replacement therapy (1). Dr. Bell believes that our explanation is insufficient and proposes that the use of ACE inhibitors, which became a widely accepted treatment for diabetic nephropathy during the second half of the study, may be principally responsible for the decline.

Several factors, however, favor our explanation. Of foremost importance, in the diabetic Pima, the age- and sex-adjusted incidence of renal replacement therapy in the second half of the study was 2.5 times (95% CI, 1.5–4.0) the rate in the first half. Only 36% (13 of 36) of those who died of diabetic nephropathy in the first half received renal replacement therapy before death, but 69% (18 of 26) received such therapy in the second half. Among the Pimas who received renal replacement therapy, survival improved significantly between 1973 and 1994, although there was only a modest increase in the number of kidney transplants (R.G. Nelson, W.C. Knowler, P.H. Bennett, unpublished observations); the death rate among those receiving renal replacement therapy declined by >50% (unpublished data). Thus, we still believe that greater access to and acceptance of renal replacement therapy and a substantial improvement in survival during therapy is largely responsible for the decline in deaths from diabetic nephropathy in this population.

ACE inhibitors were not available from the Indian Health Service Hospital that provided care to patients in this community until November 1986, and pharmacy records indicate these drugs received very limited use until September 1989. Therefore, even if we assume that ACE inhibitors postpone the development of end-stage renal disease in NIDDM (data supporting this view are derived principally from studies of IDDM), their use within the community during the study period was not sufficient to have had a major impact on mortality.

MAURICE L. SIEVERS, MD
ROBERT G. NELSON, MD, MPH
PETER H. BENNETT, MB, FRCP, FFCM

From the Phoenix Epidemiology and Clinical Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona.

Address correspondence to Maurice L. Sievers, MD, at National Institute of Diabetes and Digestive and Kidney Diseases, 1550 E. Indian School Rd., Phoenix, AZ 85014.

Reference

1. Sievers ML, Nelson RG, Bennett PH: Sequential trends in overall and cause-specific mortality in diabetic and nondiabetic Pima Indians. *Diabetes Care* 19:107–111, 1996

Pancreatic Gland Size Reduction and Exocrine Impairment in Type 1 Diabetic Children

We read with interest the letter by Chiarelli et al. (1) about ultrasound study of the pancreas in 60 young type I diabetic patients. The authors observed that the pancreatic surface was significantly smaller in IDDM patients compared with control subjects, with the most relevant reduction in adolescents. A significant positive correlation was found between the pancreatic surface area and C-peptide levels, while a negative correlation was observed between pancreatic surface area and duration of diabetes. The authors suggested that the reduced pancreatic size could be a consequence of the lack of paracrine effect of endogenous insulin (1).

Similar results were observed in our previous study (2) on pancreatic size determined by ultrasound in 15 IDDM children and adolescents (11 boys and 4 girls, ages 6.7–18.5 years and with IDDM durations from 1 month to 15 years) compared with 12 healthy control subjects.

Pancreatic evaluation was performed with a real-time–equipped Kontron Sigma 1 echograph, provided with a 5 mHz sector-scanning probe. Longitudinal and transversal scans of the pancreas were performed. The pancreas total area was measured with sonography, on transversal views, considering the axis of the splenic vein as the gage-point.

In our IDDM patients, pancreatic size was significantly lower than in control subjects (7.96 ± 3.24 vs. 13.84 ± 3.38 cm^2; $P < 0.0001$, Student's t test). In particular, this reduction in pancreatic gland area was evident in not only long-standing but also newly diagnosed patients. Age and body surface area were significantly related to pancreatic size only in the control group ($P < 0.0001$) but not in IDDM patients.

The reduction of pancreatic size, observed in diabetic patients either by autopsy (3) or by ultrasound (1,4), involves all portions of the gland, particularly the exocrine tissue, which comprises about 98% of a normal pancreas (5). It has been hypothesized that immunological or genetic factors, subclinical viral pancreatitis, or the lack of trophic (4) and paracrine (1) effect of insulin might represent causes for the shrinkage of the exocrine pancreas.

Moreover, we also found an impaired exocrine pancreatic function (6) in 21 IDDM children on the basis of a *p*-aminobenzoic acid test and the determination of fasting serum amylase, pancreatic isoamylase, lipase, trypsin, elastase, and fecal chymotrypsin.

GIUSEPPE D'ANNUNZIO, MD
ALBERTO CHIARA, MD
RENATA LORINI, MD

From the Pediatric Clinic, Università di Pavia, Pavia, Italy.

Address correspondence to Giuseppe d'Annunzio, MD, Clinica Pediatrica, IRCCS Policlinico S. Matteo, P.le Golgi, n. 2, 1-27100 Pavia, Italy.

References

1. Chiarelli F, Verrotti A, Altobelli E, Blasetti A, Morgese G: Size of the pancreas in type I diabetic children and adolescents. *Diabetes Care* 18:1504–1506, 1995
2. Lorini R, Chiara A, Rondini G, Severi F: Ecografia pancreatica in bambini e adolescenti affetti da diabete mellito insulino-dipendente. *Revista Italiana Di Pediatria* 13: 103–104, 1987
3. Foulis AK, Stewart JA: The pancreas in recent-onset type I (insulin-dependent) diabetes mellitus: insulin content of islets, insulitis and associated changes in the exocrine acinar tissue. *Diabetologia* 26:456–461, 1984
4. Fonseca V, Berger LA, Beckett AG, Dan-

dona P: Size of pancreas in diabetes mellitus: a study based on ultrasound. *Br Med J* 291:1240–1241, 1985
5. Unger RH, Foster DW: Diabetes mellitus. In *Textbook of Endocrinology*. JD Wilson and D Foster, Eds. Philadelphia, WB Saunders, p. 1255–1333
6. Lorini R, Cortona L, Scotta MS, Melzi d'Eril GV, Severi F: Exocrine pancreatic function in children and adolescents with insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 8:263–267, 1990

Pancreatic Polypeptide Response to Food and Autonomic Neuropathy in Diabetics

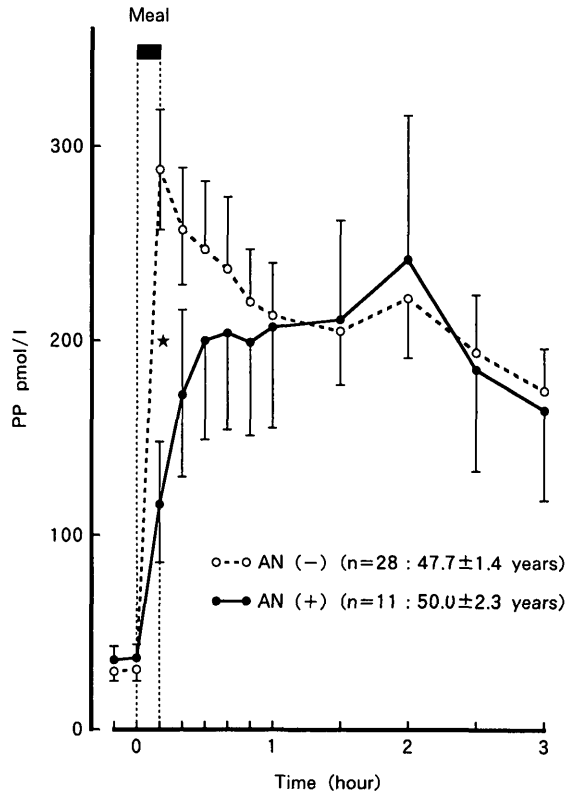

Figure 1—*Impaired PP response to meal in diabetics with autonomic neuropathy.*

Pancreatic polypeptide (PP) is a hormone under vagal control and is assumed to be a sensitive marker for vagal neuropathy (1). Previous studies have demonstrated that impaired secretion of PP serves as a marker for autonomic neuropathy in both diabetic (2,3) and nondiabetic patients. The cephalic phase of PP secretion was studied by insulin-induced hypoglycemia (2) and by sham feeding (3). However, insulin hypoglycemia may induce serious complications such as myocardial infarction in elderly people, and sham feeding is a less consistent stimulus for PP secretion. Since food is a potent stimulus for PP secretion and since autonomic neuropathy may (4) or may not affect the postprandial PP secretion, we examined the PP response to a mixed meal in diabetic patients with or without autonomic neuropathy. Autonomic neuropathy was confirmed by the presence of orthostatic hypotension and/or decreased beat-to-beat variation in heart rate by deep breathing (5). Plasma PP was measured by radioimmunoassay (6).

After loading a mixed meal (640 kcal; 36% carbohydrate, 36% fat, 28% protein), biphasic PP response was observed with the cephalic phase followed by the prolonged gastrointestinal phase, the former of which is totally under vagal control (5). As shown in Fig. 1, impaired PP secretion was observed in its cephalic, but not gastrointestinal, phase in diabetics with autonomic neuropathy. When we examined the ratio of cephalic phase PP secretion to total PP secretion ($IPPR_{40}/IPPR_{120}$; IPPR, integrated PP response), the ratio was consistent irrespective of ages from 20 to 50 in normal control subjects (0.37 ± 0.01, $n = 34$). The diabetic subjects without signs of autonomic neuropathy showed the same ratio (0.39 ± 0.07, $n = 56$), whereas diabetic subjects with autonomic neuropathy had a significantly decreased value (0.24 ± 0.02, $n = 13$, $P < 0.0005$).

Our observations demonstrate that meal loading is a safe and sensitive stimulus for detecting vagal neuropathy as far as the cephalic phase of PP secretion is concerned. The early detection of autonomic neuropathy appears to be important for retarding the advancement of the disease and for protecting patients from sudden death assumed to be caused by this complication of diabetes.

AKIO INUI, MD, PHD
NOBUHIKO MIZUNO, MD, PHD
SHIGEAKI BABA, MD, PHD, PROFESSOR EMERITUS
MASATO KASUGA, MD, PHD, PROFESSOR

From the Second Department of Internal Medicine (A.I., N.M., M.K.), Kobe University School of Medicine, Kobe; and Hyogo Medical Center for Adults, Akashi, Japan.

Address correspondence to Akio Inui, MD, PhD, Second Department of Internal Medicine, Kobe University School of Medicine, Kusunoki-cho, Chuo-ku, Kobe 650, Japan.

References

1. Schwartz TW: Pancreatic polypeptide: a hormone under vagal control. *Gastroenterology* 85:1411–1425, 1983
2. Krarup T, Schwartz TW, Hilsted J, Madsbad S, Verlaege O, Sestoft L: Impaired response of pancreatic polypeptide to hypoglycemia: an early sign of autonomic neuropathy in diabetics. *Br Med J* 15:1544–1546, 1979