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Decrease in Mortality from Diabetic Nephropathy in Pima Indians

Silvers et al. (1) report a decrease in death rate in Pima Indians from diabetic nephropathy when comparing the years 1975–1982 with 1983–1989. They attribute this decline to improvements in renal replacement therapy.

Even with adequate dialysis, the prognosis remains abysmal for end-stage diabetic nephropathy even in younger people (2), and unless a significant number of transplants were performed, it would seem unlikely that improvement in renal replacement therapy would explain a 44.4% decline in the death rate from diabetic nephropathy.

A more likely reason for this improvement would be the use of ACE inhibitors, which were not used for diabetic nephropathy during the first period but became standard of care during the second period. By postponing the development of end-stage renal disease, the increased frequency of ischemic heart disease associated with early diabetic nephropathy (3) and the increasing age of the diabetic subjects would account for the swing toward ischemic heart disease as a cause of death.

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Precocious and Exaggerated Seric IgA Production in Children Affected by IDDM

The role of autoimmunity in the pathogenesis of IDDM is well known (1). Among the initially recognized markers for autoimmune disease is an immunoglobulin deficiency or excess attributed to dysregulated "T-dependent" B-cell activation (2). Conflicting data have been reported on the abnormalities of immunoglobulin secretion in IDDM. Some studies show lower levels of IgG, IgA, and IgM at the onset of disease, followed by a gradual normalization (3). Meanwhile, abnormal serum immunoglobulin concentrations in patients with IDDM have been described by others, mainly as influenced by the degree of glycemic control (4,5). Furthermore, because few data are available in young patients affected by IDDM, we investigated the serum levels of IgA, IgG, and IgM in 92 IDDM patients (57 male, 35 female) who had a duration of the disease that ranged from 0.1 to 6.0 years and in which any concomitant infection was ruled out by physical and biochemical examination. HbA_{1c} levels ranged from 7.8 to 11% (normal value 3.5–6.5%) and fructosamine levels ranged from 245 to 450 μmol/l (normal value <285 μmol/l). The patients were divided into two age-groups based on the pattern of distribution of immunoglobulins in the Italian pediatric population (ages 1–5 years and 5–12 years old, respectively) (6): group A (20 patients, 3.4 ± 0.9 years old) and group B (72 patients, 8.8 ± 2.0 years old). The results (expressed as means ± SD) were compared with a local population of 62 sex- and age-matched healthy control subjects. Comparisons between groups were made with the Mann-Whitney nonparametric test for the abnormally distributed variables.

IgG and IgM levels in patients did not statistically differ from those in control subjects, whereas IgA levels showed a peculiar pattern. Both group A (IgA, 113 ± 61 mg/dl) and group B (178 ± 75 mg/dl) showed higher levels of IgA when compared with their matched control groups (IgA, 73 ± 30, $P < 0.02$; IgA, 121 ± 54, $P < 0.001$, respectively). Moreover, when the IgA values from the diabetic children or the control subjects were expressed as percentages of mean adult values (6), it resulted an exaggerated and precocious pattern of IgA maturation in most IDDM patients (group A 83 ± 45% vs. control subjects 54 ± 22%, $P < 0.02$; group B 131 ± 55% vs. control subjects 95 ± 40%, $P < 0.001$). On the contrary, three patients had a total deficit (<5 mg/dl) and two a partial deficit (<30 mg/dl) of IgA. No correlation was found between IgA levels and the duration of the disease or the parameters of metabolic control.

In our investigation, we found that IgA production may be influenced in one direction or another in IDDM patients. The incidence of selective IgA deficiency is in agreement with that reported by Smith et al. (7). The age of the three patients affected by IgA deficit (12 years) excludes a transient immaturity of production and suggests an HLA-associated defect, as previously described (7). The presence of abnormal serum IgA concen-

tration in a large population of IDDM children, the previous attainment of the mean adult values, and the lack of correlation of these levels with the duration of the disease and metabolic control indicate that the aberrant immune response may have a substantial pathogenetic link with IDDM. Furthermore, quantitative and qualitative longitudinal studies are required to clarify the potential mechanism involved, because neither the cause of this phenomenon nor its implications for monitoring diabetes are known.

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Table 1

Type of treatment	Cumulative follow-up (patient-year)	HbA_{1c} (%)	Severe hypoglycemia (mean per patient-year)	*n*
Group 1	51	8.1 ± 0.1	0.69	35
Multiple injections	20	8.2 ± 0.2	0.99	
External pump	28	7.9 ± 0.1	0.29	
Group 2	214	7.7 ± 0.1*	0.11*	23

HbA_{1c} is mean ± SE. *$P < 0.001$ vs. subcutaneous administration.

Decreased Severe Hypoglycemia Frequency During Intraperitoneal Insulin Infusion Using Programmable Implantable Pumps

The Diabetes Control and Complications Trial (DCCT) study (1) has shown that subcutaneous intensive insulin therapy minimizes microvascular complications by lowering HbA_{1c} levels but dramatically increases severe hypoglycemia frequency. A previous Evadiac group report (2) showed that intraperitoneal insulin infusion significantly decreased both HbA_{1c} levels and severe hypoglycemia frequency when comparing retrospectively preimplant subcutaneous therapy data to postimplant data in a longitudinal study.

In this prospective trial, the frequency of severe hypoglycemia has been determined in 240 type I C-peptide–negative patients. All patients were treated with an implantable pump before the study. Group 1 (n = 120) was switched to subcutaneous therapy using an external pump (n = 55) or multiple injections (n = 59) because of technical pump or catheter dysfunction mainly due to insulin aggregate formation in the device. Group 2 (n = 120) remained under intraperitoneal implantable pump therapy. Metabolic results are summarized in Table 1.

Statistical tests used were the Student's t test for HbA_{1c} comparison and comparison of two frequency test for hypoglycemia data. Despite a statistically better metabolic control in group 2, the severe hypoglycemia frequency is significantly lower than in group 1. Severe hypoglycemia frequency in group 1 is higher than previously described (2) but remains comparable to the DCCT data. Part of this increase may be explained by the recent change in therapy. The same difference is observed in group 2, the patients have now been treated with an implantable pump for a long time and may be less careful regarding their diabetes control than in the first study.

Continuous subcutaneous insulin infusion tends to induce hypoglycemias less than multiple injections.

Although hypoglycemia frequency was higher than in our previous report and our study was not randomized, the results confirm that intraperitoneal therapy decreases the risk of severe hypoglycemia in spite of HbA_{1c} improvement. However, insulin aggregate formation needs to be solved before considering intraperitoneal therapy as an alternative to subcutaneous therapy. Improved insulin formulations are currently under evaluation.

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