Rapid Publications

Diazoxide Treatment at Onset Preserves Residual Insulin Secretion in Adults with Autoimmune Diabetes

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Twenty islet cell antibody (ICA)-positive patients, aged 19–38 years, with IDDM were randomized at onset to treatment with either diazoxide, a K^+ channel opener that inhibits the release of insulin, or placebo for 3 months, in addition to multiple insulin injection therapy. The patients who were given diazoxide displayed higher residual insulin secretion than the placebo group after 1 year (basal C-peptide level, 0.40 ± 0.04 vs. 0.25 ± 0.04 [mean ± SE] nmol/l; $P < 0.021$) and at an 18-month follow-up (0.37 ± 0.06 vs. 0.20 ± 0.01 nmol/l, $P < 0.033$). Metabolic control did not differ between the two groups. During the course of the study, no differences in islet cell or GAD autoantibodies were detected between the two groups. The results of this study warrant further trials to explore the potential of inducing target cell rest in order to halt the loss of insulin-producing cells during the early course of the disease. ***Diabetes*** **45:1427–1430, 1996**

Upon the initiation of insulin therapy in IDDM, the patients frequently experience a period of temporary remission, with improved insulin production and a decreased need for exogenous insulin. The reason for this partial recovery of islet function is probably caused by multiple factors. An inhibitory effect of hyperglycemia on insulin production (1) is removed by controlling hyperglycemia. One can also speculate that remission reflects a temporary alleviation of the destructive autoimmune process, since β-cell antigen expression is enhanced by high glucose concentrations both in vitro (2–4) and in vivo (5,6). It has been shown earlier that short-term diazoxide treatment may lead to some recovery of insulin secretion in IDDM patients (8), and we have shown that the intensity of insulin secretion is correlated with the amount of islet cell antigen expressed in vitro (7) and in vivo (6). On this basis, we designed a randomized prospective clinical trial of supplementary treatment with diazoxide, a K^+ channel opener that inhibits the release of insulin (9), compared with placebo, that was given during the first 3 months following the clinical onset of autoimmune diabetes.

RESEARCH DESIGN AND METHODS

Patients. Twenty patients (15 males and 5 females, aged 19–38 years) with IDDM, diagnosed on the basis of clinical criteria and the presence of islet cell antibodies in the serum, were randomized to treatment with either diazoxide (4–6 mg per kg of body weight in divided oral doses; Avondale Company, Rathdrum, Ireland) or placebo in addition to insulin for 3 months. Treatment with diazoxide was initiated within 1 week after arrival at the hospital. All patients received multiple insulin injections (regular insulin at mealtimes and NPH insulin at bedtime). They were all introduced to the concepts of self-monitoring blood glucose and adjusting insulin dosage. The patients were hospitalized during the initial 5–8 days and then followed up as outpatients after 14 days and 1, 3, 6, 9, 12, and 18 months of the study. Endogenous insulin release, metabolic control, and the autoantibody titers were monitored at regular intervals. The protocol was approved by the human ethics committee of the hospital.

Hormone assays. Endogenous insulin release was determined by measurements of basal and glucagon-stimulated C-peptide concentrations. Serum C-peptide concentrations were measured by radioimmunoassay in routine use. Glucagon stimulation tests were performed in the morning before breakfast, and blood was drawn at 0 and 6 minutes after intravenous injections of 0.5 mg glucagon. Blood glucose levels were checked before the tests and ranged between 5 and 9 mmol/l in all instances. HbA_{1c} was determined by high-performance liquid chromatography (normal range, 3.5–6.0%).

Autoantibody measurements. Islet cell antibodies (ICAs) were determined by immunofluorescence, and the antibody titers, expressed in Juvenile Diabetes Foundation (JDF) Units using the JDF reference serum as standard according to the Fifth ICA Exchange Proficiency Program. GAD autoantibodies were analyzed by a radioligand assay, and the titers were expressed as a GAD_{65} index (10). At diagnosis, the ICA titers of the diazoxide and placebo groups did not differ (40 [median] and 20–320 [range] vs. 40 and 5–1280, respectively), nor did the GAD_{65} indexes (0.18 [median], 0–1.65 [range] vs. 0.15 and 0–1.28, respectively).

Statistics. The differences between the two groups were analyzed by the nonparametric Mann-Whitney test.

RESULTS

At the clinical onset of disease, all the patients displayed hyperglycemia and a reduced insulin production as reflected by low C-peptide levels. Mean HbA_{1c} was 10.1% and the range was 7.1–15.4% (Table 1). Eleven (five in the diazoxide- and six in the placebo-treated groups) of the 20 patients presented with ketonuria.

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ICA, islet cell antibody; JDF, Juvenile Diabetes Foundation.

TABLE 1
Characteristics of patients with newly manifested autoimmune diabetes at onset of clinical disease and at follow-up

	Age/sex	BMI (kg/m^2)	HbA_{1c} (%)	Insulin dose (U/kg)	C-peptide (nmol/l)	
					Basal	Stimulated
Diazoxide						
1	19/M	20.2/23.7	15.4/5.4	0.89/0.26	0.28/0.55/0.61	0.33/0.71/0.72
2	37/M	21.8/22.9	8.7/6.6	0.46/0.46	0.71/0.59/0.57	0.79/0.84/0.82
3	21/F	19.5/20.7	8.0/5.1	0.18/0.22	0.27/0.51/0.48	0.34/0.75/0.70
4	26/M	22.8/24.8	14.4/6.4	0.68/0.71	0.27/0.51/0.48	0.43/0.86/0.79
5	30/M	20.6/22.3	9.3/4.1	0.56/0.36	0.20/0.21/0.24	0.26/0.27/0.40
6	28/M	16.7/16.6	7.1/9.5	0.66/1.40	0.32/0.40/0.13	0.48/0.56/0.20
7	38/M	20.1/18.4	9.7/4.0	0.20/0.18	0.40/0.28/nd	0.46/0.33/0.74
8	35/F	20.5/24.8	7.9/7.0	0.66/0.57	0.19/0.19/0.15	0.40/0.48/0.30
9	31/M	24.9/26.5	12.5/8.3	0.65/0.80	0.21/0.36/0.30	0.40/0.54/0.44
10	31/M	21.8/23.8	9.8/7.2	0.65/0.39	0.13/0.43/0.35	0.33/0.63/0.59
Mean	29.6	20.9/22.5	10.3/6.4	0.56/0.53	0.30/0.40/0.37	0.42/0.60/0.57
Placebo						
1	31/M	20.0/23.6	10.7/6.3	0.67/0.50	0.24/0.43/0.21	0.30/0.56/0.30
2	26/M	24.8/27.4	8.0/8.0	0.67/0.78	0.24/0.13/0.13	0.30/0.14/0.14
3	31/F	21.5/24.6	12.1/9.0	0.65/0.70	0.34/0.23/0.10	0.35/0.26/0.13
4	27/M	19.3/20.2	8.6/7.7	0.52/0.61	0.23/0.17/0.24	0.35/0.29/0.25
5	31/M	28.2/23.6	10.3/4.9	0.29/0.00	0.44/0.39/nd	0.56/0.67/0.70
6	20/M	21.2/21.7	11.2/7.9	0.59/0.70	0.22/0.10/0.10	0.29/0.13/0.10
7	25/M	21.9/24.7	8.0/5.0	0.37/0.42	0.22/0.38/0.32	0.56/0.64/0.59
8	26/M	23.3/26.4	10.3/5.5	0.65/0.45	0.25/0.27/0.40	0.28/0.47/0.70
9	20/F	21.4/22.5	11.6/4.6	0.95/0.58	0.35/0.27/0.24	0.37/0.46/0.37
10	33/F	21.6/22.4	8.6/6.9	0.51/0.52	0.23/0.12/0.10	0.37/0.13/0.13
Mean	27.0	22.3/23.7	9.9/6.6	0.59/0.53	0.28/0.25/0.20	0.37/0.38/0.34

Data are for start/18-month follow-up or start/12-/18-month follow-up, unless otherwise indicated. The patients were given diazoxide (n = 10) or placebo (n = 10) during the initial 3-month period.

Upon the initiation of insulin injections, the group of patients taking the placebo showed a partial recovery of the C-peptide levels, which peaked ~1–3 months following diagnosis, followed by a decline. The diazoxide-treated group displayed a different pattern. An inhibition of the endogenous insulin production was seen at 1 month of therapy and was also apparent at the end of 3 months of medication. Thereafter, the C-peptide levels showed an improvement that continued beyond 1 year after the onset of disease (Fig. 1). The basal and stimulated levels showed parallel patterns. The differences in the C-peptide levels between the diazoxide- and placebo-treated groups were significant at 12 months (basal levels: 0.40 ± 0.04 vs. 0.25 ± 0.04 nmol/l, $P < 0.021$; stimulated levels: 0.60 ± 0.06 vs. 0.38 ± 0.06 nmol/l, $P < 0.031$) and at 18 months (basal levels: 0.37 ± 0.06 vs. 0.20 ± 0.01 nmol/l, $P < 0.033$; stimulated levels: 0.57 ± 0.05 vs. 0.34 ± 0.08 nmol/l, $P < 0.023$).

Throughout the study, daily insulin doses were adjusted according to the patient's self-monitoring of his or her blood glucose levels to achieve optimal glucose control. The hyperglycemia at the onset of the disease was rapidly corrected, as reflected by a similar decline in HbA_{1c} in both groups. Glycemic control did not differ between the diazoxide and placebo groups (HbA_{1c} at 1 year 5.7 ± 0.4 and 6.4 ± 0.5% and at 18 months 6.4 ± 0.6 and 6.6 ± 0.5%, respectively). The islet cell and GAD autoantibody levels changed only slightly during the year of the study (data not shown), and no significant differences were found between the titers at onset and those at follow-up.

Adverse effects. The intake of diazoxide was accompanied by reversible side effects in nine of the ten patients. In one case, the drug was discontinued after 2 months of therapy; in another case, the dose was reduced. Edema was noted in six of the patients, and in four of these, a low dose of thiazide diuretics was given with good response. Two patients complained of headache. Two patients experienced slight diarrhea, and three patients noted increased hair growth at the end of the study. No side effects were reported in the placebo-treated group.

DISCUSSION

In this study of adult patients with newly manifested autoimmune diabetes, 3 months of supplementary treatment with diazoxide resulted in an improved endogenous insulin production. The C-peptide level differed significantly from that of the placebo-treated control group at 12 and 18 months. This finding is of interest since it has been previously shown that the presence of minute residual β-cell function in patients with long-term IDDM confers better glycemic control (11–13), which in itself according to the evidence presented from the Diabetes Control and Complications Trial is associated with a remarkable reduction in the risk of long-term complications (14). In the present study of 20 patients, no difference in metabolic control between the two treatment groups was observed. It appears likely that a study of a larger patient population and a longer follow-up period would demonstrate an improved metabolic

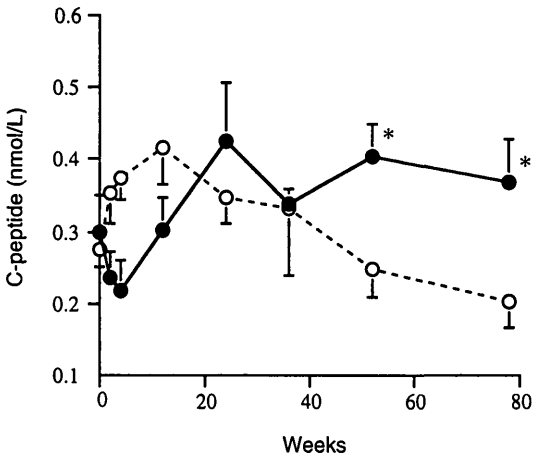

FIG. 1. Endogenous insulin secretion in two groups of 10 patients, each with newly manifested autoimmune diabetes and receiving placebo (○) or diazoxide (●) supplementation during an initial 3-month period in addition to multiple insulin injections. Basal C-peptide levels (mean ± SE) are illustrated.

status that is associated with a better preserved endogenous insulin production.

Diazoxide given orally is usually administered in doses exceeding those of the present study to inhibit excessive insulin secretion in insulinoma (15) or nesidioblastosis (16). The drug acts by opening ATP-sensitive K^+ channels of the β-cell (9), but it also has extra-pancreatic effects (e.g., on sodium and water balance) (17). The inhibitory effect of diazoxide on insulin secretion was particularly noted after 1 month of treatment. After 3 months, the inhibition was less marked, possibly reflecting a recovery of the secretory capacity of the β-cells or diminished patient compliance, although this was specifically asked of and denied by all patients. The doses of exogenous insulin that were administered during the 3-month periods did not differ between the two groups. This possibly reflects some extra-pancreatic action of diazoxide. For instance, the drug has a vasodilator effect and might alter insulin sensitivity through such a mechanism (e.g., muscle blood flow has been shown to modulate insulin-mediated glucose uptake) (18).

Our study was based on the hypothesis that target cell rest is likely to reduce the intensity of an autoimmune destructive process. Thyroxine supplementation in hypothyroid patients with autoimmune thyroiditis reduces autoantibody levels (19,20), presumably by lowering thyrocyte activation via the thyroid-stimulating hormone receptor. Likewise, in autoimmune thyrotoxicosis due to Graves' disease, methimazole and perchlorate induce remission of the disease by blocking thyroid peroxidase and iodide uptake, respectively (21). Previously, we (2,3,6) and others (4,5) have demonstrated a relationship between glucose stimulation of islet cell activity and the amount of islet cell autoantigen expressed, and have found that inhibition of insulin secretion reduces autoantigen expression (7). Therefore, we suggest that the better preservation of β-cell function observed after diazoxide therapy is attributable to target cell rest induced by the treatment. The inhibition of secretion might not only reduce antigen exposure but also support nonimmunological mechanisms of cellular repair (22).

It has been reported that low-dose insulin administration to first-degree relatives results in a reduced risk of developing autoimmune diabetes (23). The mechanism of this phenomenon is not clear, but target cell rest may contribute. Our present results with diazoxide are encouraging as an alternative way of preserving β-cell function. In the future, modified protocols and extended trials, including subjects with subclinical disease also, will be of interest to study.

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