Secondary Failure to Treatment with Oral Antidiabetic Agents in Non-insulin-dependent Diabetes

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To study the etiopathogenesis of secondary drug failure to treatment with oral antidiabetic agents in patients with non-insulin-dependent diabetes (NIDD) we compared 60 "nonresponders" with 60 "responders" to treatment with oral drugs. Secondary drug failure was defined as mean diurnal blood glucose >12 mmol/L after an initial good response of ≥2 yr. The nonresponders were characterized by 50% lower C-peptide concentrations than the responders ($P < 0.001$). We could not, however, define a critical C-peptide level to discriminate between patients requiring and not requiring insulin therapy. There was a wide overlap of individual C-peptide values between responders and nonresponders that attenuates the clinical value of single C-peptide measurements in predicting therapy. Only by serial measurements over a period of time was it possible to achieve information about changes in beta cell function. The nonresponders showed increased frequency of islet cell ($P < 0.01$), thyroid antimicrosomal ($P < 0.01$), and gastric parietal cell antibodies ($P < 0.02$). In nonresponders, HLA-antigen B8 was increased ($P < 0.05$) and HLA-B7 decreased ($P < 0.01$) compared with frequencies of responders. In conclusion, impaired beta cell function is a characteristic feature of many, but not all, NIDD patients who fail on treatment with oral antidiabetic drugs. The presence of islet cell and thyrogastric antibodies can unmask a distinct group of NIDD patients with a high risk of secondary drug failure and subsequent insulin dependency. HLA typing may further help to predict secondary failure in NIDD. DIABETES CARE 1986; 9:129–33.

Secondary failure to treatment with oral antidiabetic drugs is the term used to characterize patients who, after an initial good response of ≥1 mo find the oral drugs becoming gradually ineffective.[1,2] The annual rate of secondary drug failure ranges from 3% to 30%[3] and increases with duration of diabetes.[4] The underlying mechanisms are still uncertain, although deterioration of beta cell function has been suggested as a causative factor.[5,6] There are as yet no studies confirming this suggestion. It is obvious that the above definition of secondary drug failure is inconceivable, since it would include many patients with insulin-dependent diabetes (IDD) in the phase of remission. We have therefore extended the period of drug response to ≥2 yr, after which mean diurnal blood glucose values >12 mmol/L denote secondary drug failure. A prerequisite is however that reasons such as intercurrent illness and diet failures have been ruled out. Using this definition we have compared 60 "nonresponders" to treatment with oral antidiabetic drugs with 60 "responders" to oral drug therapy to study the etiopathogenesis of secondary drug failure in non-insulin-dependent diabetes (NIDD).

MATERIALS AND METHODS

Among patients admitted to the Helsinki University Central Hospital for evaluation of secondary failure to treatment with oral hypoglycemic drugs, 60 patients fullfilled the criteria for true secondary drug failure, i.e., exclusion of cases with intercurrent illness or poor dietary adherence, and were selected for the study. These patients (nonresponders) were compared with a group of 60 NIDD patients still responding to treatment with oral hypoglycemic agents (responders). The two patient groups were matched for age and age at diagnosis of diabetes (Table 1). All patients had nonketotic diabetes that had been diagnosed between the ages of 35 and 65 yr and had been in acceptable glycemic control during treatment with oral hy-

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poglycemic agents for ≥2 yr. Patients with secondary diabetes or with recent myocardial infarction or renal or hepatic dysfunction were excluded. Nonresponders had been treated with glibenclamide (glyburide) or glipizide in doses of 15–25 mg/day (54 patients), 2 g/day tolbutamide (2 patients), and 500–750 mg/day chlorpropamide (4 patients). Forty patients were additionally given 1–2 g/day metformine. Responders were treated with glibenclamide or glipizide (mean dose 10 mg/day, 54 patients), 0.5–1 g/day tolbutamide (3 patients), and 250–500 mg/day chlorpropamide (3 patients). Six responders were additionally treated with 0.5–1 g/day metformine.

Poor response to treatment with oral hypoglycemic drugs was defined as mean diurnal blood glucose values >12 mmol/L (216 mg/dl, mean of at least four measurements per day

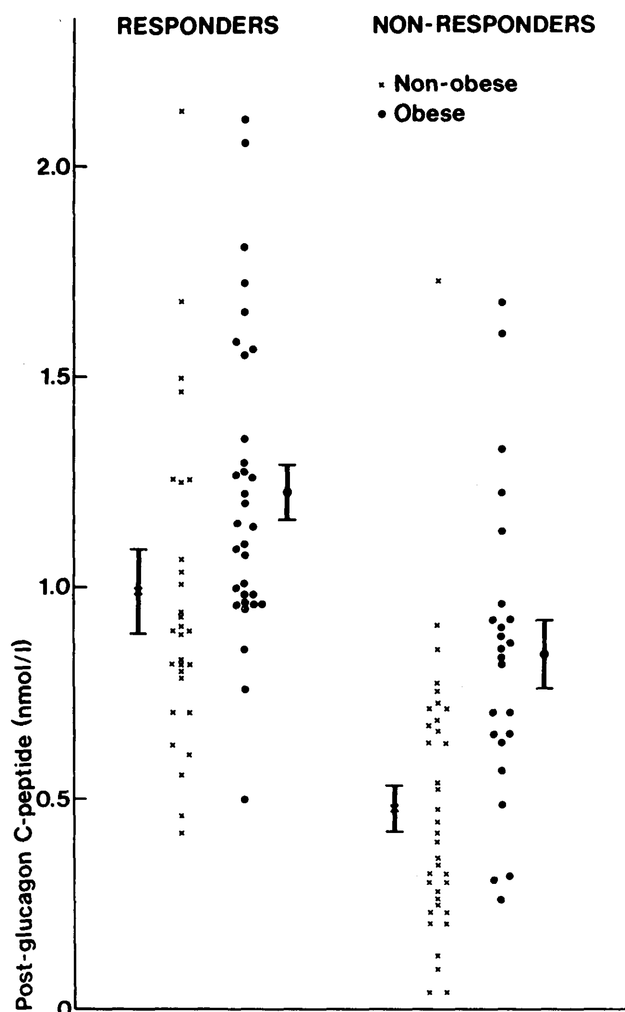

FIG. 1. Individual C-peptide response to 1 mg glucagon i.v. in nonobese (body weight <120% of ideal) and obese (body weight >120% of ideal) responders (left panel) and in nonobese and obese nonresponders (right panel) to treatment with oral antidiabetic drugs. The values of nonresponders were obtained before starting insulin therapy. Vertical lines show mean ± SEM for each group.

TABLE 1
Clinical characteristics of patients

	Responders	Nonresponders
N (women/men)	60 (28/32)	60 (28/32)
Family history of NIDD (%)	56.7	49.2
Family history of IDD (%)	10.0	15.8
Age (yr)	56.4 ± 1.0	56.5 ± 0.9
Age at onset (yr)	48.5 ± 1.0	48.2 ± 0.9
Relative body weight (%)	117 ± 2	107 ± 2*

Mean ± SEM.
*P < 0.001 versus responders.

determined in the hospital after controlling diet). All these patients presented with fasting blood glucose values >10 mmol/L (180 mg/dl). Responders all showed good glycemic control as indicated by stable fasting blood glucose concentrations <9 mmol/L (160 mg/dl) and/or glycohemoglobin concentrations <10% during a follow-up period of ≥2 yr (measured at least four times during this period). Fasting blood glucose concentrations from the time nonresponders still responded to treatment with oral hypoglycemic agents were drawn from patient hospital records (Figure 1). All nonresponders presented to the outpatient clinic of Helsinki University Central Hospital for evaluation of response to treatment with oral hypoglycemic agents. Thereafter the patients were followed in the outpatient clinic for a period of 6–12 mo, during which time they received personal dietary instructions and measures were taken to optimize oral drug therapy and exclude other possible reasons for poor glycemic control. If glycemic control did not improve during this period they were admitted to the hospital for further evaluation of drug response. In the hospital all patients received an isocaloric diabetes diet consisting of 45% carbohydrate, 35% fat, and 20% protein. Patients with mean diurnal blood glucose >12 mmol/L under these conditions were considered as being nonresponders and were subjected to an insulin treatment program in accordance with the clinical routine. Of 72 patients admitted to the hospital for evaluation of poor response to treatment with oral drugs, 12 significantly improved glycemic control during hospitalization and were excluded from the study. The mean insulin dose (±SEM) of the patients at discharge from hospital was 37 ± 3 IU (range 12–128 IU). After starting insulin therapy, nonresponders were followed in the outpatient clinic for ≥1 yr.

Responders were followed in the outpatient clinic for a period of ≥2 yr. Only those patients whose glycemic control remained stable and within the criteria for responders were included in the control group. All subjects gave informed consent for the study and the protocol was approved by the Ethical Committee of the Helsinki University Hospital.

The clinical characteristics of the patients are shown in Table 1. Patients were considered to have a positive family history for NIDD or IDD if there was another family member with the disease. Relative body weight was calculated using ideal body weight values for the Finnish population.[7] At the

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beginning of the study, determinations of HLA antigens and thyrogastric and islet cell antibodies were performed. Beta cell function was assessed at regular intervals by measuring C-peptide concentrations in serum before and after i.v. injection of 1 mg glucagon.[8] Serum C-peptide was analyzed using the radioimmunoassay method described by Heding.[9] Blood glucose was measured by a glucose-oxidase method adapted for autoanalyzer, and glycohemoglobin (HbA_1) was measured by microcolumn chromatography.[10] Islet cell antibodies (ICA) and gastric parietal cell antibodies were detected using indirect immunofluorescence with undiluted sera and complement fixation techniques (CF-ICA).[11] Thyroid antimicrosomal and thyroglobulin antibodies were titrated by passive hemagglutination using Welcome Thyme (Wellcome Laboratories, Beckenham, U.K.) kits. HLA typing was performed by standard two-stage microcytotoxicity method using a total of 120 antisera defining 11 A-loci, 20 B-loci, and 6 C-loci. Eight DR specifities were determined using a minimum of 60 antisera.[12]

Values are expressed as means ± SEM. Statistical analysis was carried out by the use of Student's *t*-test for unpaired and paired data and chi-square test or Fisher's exact probability test, where appropriate. Correlations were tested by linear regression analysis.

RESULTS

Glycemic control. Fasting blood glucose and HbA_1 concentrations of nonresponders were 13.9 ± 0.4 mmol/L and 13.3 ± 0.3%, respectively, before starting insulin therapy. Although insulin therapy was associated with a marked improvement in glycemic control, blood glucose and HbA_1 concentrations during insulin therapy were still higher than corresponding values of responders (7.1 ± 0.2 mmol/L and 8.9 ± 0.2%, respectively) ($P < 0.01$).

Beta cell function. Basal and postglucagon C-peptide concentrations were ≈50% lower in nonresponders (0.38 ± 0.02 nmol/L and 0.58 ± 0.06 nmol/L, respectively) than in responders (0.60 ± 0.04 nmol/L and 1.02 ± 0.06 nmol/L, respectively) ($P < 0.001$) at the beginning of the study. Stimulated C-peptide concentrations of nonresponders decreased significantly during the follow-up period to 0.48 ± 0.05 nmol/L ($P < 0.01$), whereas there was no change in glucagon-stimulated C-peptide concentrations of responders during this period (1.04 ± 0.08 nmol/L at the end of follow-up). The glucagon-stimulated C-peptide concentrations were positively correlated with body weight in nonresponders ($r = 0.47$, $P < 0.001$) but not in responders ($r = 0.13$). The decrease in HbA_1 concentrations after starting insulin therapy was negatively correlated with the postglucagon C-peptide concentrations ($r = -0.47$, $P < 0.01$). There was a wide overlap of individual C-peptide values between responders and nonresponders even if the two groups were clearly separated by mean basal and glucagon-stimulated C-peptide concentrations (Figure 1). Obese responders (body weight >120% of ideal) showed clearly higher stimulated C-peptide concentrations than nonobese responders (body weight <120% of ideal) (1.23 ± 0.06 nmol/L versus 0.99 ± 0.10 nmol/L, $P < 0.05$), and this difference was magnified between obese and nonobese nonresponders (0.84 ± 0.08 nmol/L versus 0.48 ± 0.05 nmol/L, $P < 0.001$).

Organ-specific antibodies. Positive titers for ICA and CF-ICA were found more frequently among nonresponders than among responders ($P < 0.01$). Eight of 12 ICA–positive (66.7%) and 5 of 8 CF-ICA–positive (62%) nonresponders had normal weight, whereas all 3 ICA–positive responders were obese. ICA–positive nonresponders presented with lower stimulated C-peptide concentrations than ICA–negative nonresponders (0.44 ± 0.10 nmol/L versus 0.68 ± 0.06 nmol/L, $P < 0.02$). Furthermore, the reduction in HbA_1 after starting insulin was greater in ICA–positive than in ICA–negative patients (6.5 ± 0.5% versus 4.5 ± 0.5%, $P < 0.05$). Nonresponders also showed higher frequencies of thyroid antimicrosomal ($P < 0.01$) and gastric parietal cell antibodies ($P < 0.05$) than responders but the frequencies of thyroglobulin antibodies did not differ between the two groups (Table 2).

HLA antigens. The frequencies of certain HLA antigens known to be positively or negatively associated with IDD are shown in Table 3. HLA-B7, the frequency of which is reduced in IDD, was less prevalent in nonresponders than in responders ($P < 0.01$). The frequency of DR2, which is in

TABLE 2
Frequency of islet cell and thyrogastric antibodies

	Responders		Nonresponders	
	N	%	N	%
Islet cell antibodies (ICA)	3/58	5.2	12/53	22.6*
Islet cell antibodies (CF-ICA)	1/58	1.7	8/53	15.0*
Thyroid antimicrosomal antibodies	4/60	6.7	14/54	25.9*
Thyroglobulin antibodies	4/60	6.7	7/54	13.0
Gastric parietal cell antibodies	8/58	13.8	17/56	30.4†

*$P < 0.01$; †$P < 0.05$ versus responders.

TABLE 3
Frequencies of certain HLA antigens

	Responders		Nonresponders	
HLA antigen	N	%	N	%
B7	18/60	30.0	6/59	10.2*
B8	8/60	13.3	19/59	32.2†
B15	18/60	30.0	12/59	20.3
B8/B15	2/60	3.3	4/59	6.8
DR2	12/37	32.4	8/36	22.2
DR3	13/37	35.1	15/36	41.7
DR4	15/37	40.5	18/36	50.0
DR3/DR4	6/37	16.2	8/36	22.2

Chi-square test: *$P < 0.02$ versus responders; †$P < 0.01$.

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positive linkage disequilibrium with B7, tended to be lower in nonresponders than in responders (NS). The frequency of HLA-B8, which is increased in IDD, was increased in nonresponders ($P < 0.05$). The frequencies of other HLA-A-/B-, C-, or DR- antigens did not differ significantly between the groups.

DISCUSSION

We measured beta cell function as C-peptide response to glucagon because it is a simple and reproducible test[13] that also allows assessment of beta cell function after starting insulin therapy. There is a close correlation between C-peptide response to glucagon and to meals in NIDD patients ($r = 0.83$, $P < 0.001$),[13] which does not necessarily mean that the test also reflects insulin response to meals. However, a recent report showed that beta cell function can be estimated from peripheral C-peptide measurements in the dog.[14]

It has been generally accepted that deterioration of beta cell function is the main cause of secondary drug failure to treatment with oral antidiabetic agents in patients with NIDD. Our findings of reduced C-peptide response to glucagon in nonresponders add indirect support to this view. They do not prove a causal relationship between impairment in beta cell function and secondary drug failure because there are insufficient data concerning C-peptide from onset of the disease. It is obvious that insulin represents the treatment of choice in these patients, since the lower the C-peptide, the greater was the improvement in glycemic control after starting insulin. From a clinical standpoint it would be important to know the critical C-peptide level below which insulin therapy should be initiated. Madsbad et al.[15] have suggested that a postglucagon C-peptide value of 0.6 nmol/L can discriminate between patients who require insulin and those who do not; we could not confirm this statement. Instead we found a wide overlap of individual glucagon-stimulated C-peptide values between the two groups. There may be several explanations for these differences, e.g., mode of treatment, duration of diabetes, and differences in body weight. Body weight should be considered when interpreting C-peptide results, as seen from the positive correlation between body weight and postglucagon C-peptide concentrations in nonresponders. In keeping with this we found higher C-peptide concentrations in obese nonresponders than in nonresponders with normal weight. When compared with weight-matched obese responders, obese nonresponders showed decreased glucagon-stimulated C-peptide concentrations, suggesting that obese patients can show a relative impairment of beta cell function even when absolute values are apparently normal. Due to the wide overlap of postglucagon C-peptide values a single C-peptide measurement is of limited value in the search for future candidates for insulin therapy; we merely need serial measurements over a period of time. As seen in Figure 1, a continuous fall in postglucagon C-peptide concentrations is a characteristic feature of secondary drug failure. It is obvious, however, that impaired beta cell function cannot explain all cases of secondary drug failure in NIDD. Insulin resistance is a consistent characteristic of NIDD and is usually aggravated by obesity.[16,17] It is therefore likely that the obese nonresponders with apparently normal C-peptide levels presented with some degree of insulin resistance. This is at least partially supported by studies showing a negative correlation between glycemic control and insulin sensitivity in patients with NIDD.[13,18]

Except for lower body weight there were no clinical signs to discriminate between responders and nonresponders. In the search for markers of subsequent secondary drug failure we found increased frequencies of islet cell and thyrogastric antibodies in nonresponders. Increased frequency of islet cell antibodies in patients with secondary drug failure has been previously reported by Irvine et al.[19] We now add direct support to the view that secondary drug failure in ICA–positive NIDD patients is due to insulin deficiency. This subgroup of nonresponders with a high frequency of organ-specific antibodies seems to represent a distinct entity within the spectrum of NIDD. Most of them are women with high prevalence of ICA, thyrogastric autoimmunity, and progressive beta cell damage. We have recently proposed the introduction of a new subgroup of NIDD, "pseudotype 2 diabetes" or "latent type I diabetes," to describe these patients.[20] The HLA pattern of nonresponders was not unlike that seen in IDD, i.e., increased frequency of HLA-B8 and decreased frequency of HLA-B7. The lack of differences in DR antigens may be ascribed to the relatively small number of DR-typed patients in the groups. These findings lend support to the view that some of the NIDD patients who develop secondary drug failure genetically represent IDD.

In conclusion, impaired beta cell function is a characteristic feature of many, but not all, NIDD patients who fail on treatment with oral antidiabetic drugs. Insulin resistance may play a role in the pathogenesis of secondary drug failure in obese patients with normal beta cell function. Prospective studies with sequential measurements of beta cell function and insulin sensitivity from onset of diabetes to diagnosis of drug failure are needed to quantitate the relative contribution of these factors to secondary drug failure in NIDD. The presence of ICA and thyrogastric antibodies can unmask a distinct group of NIDD patients with a high risk of secondary drug failure and subsequent insulin requirement. HLA typing may further help to predict secondary drug failure in NIDD, since certain HLA antigens are more frequently seen among patients who fail on treatment with oral antidiabetic drugs.

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