Diabetologia (1981) 20: 530–534

Diabetologia

Effect of Strict Blood Glucose Control on Residual B-Cell Function in Insulin-Dependent Diabetics

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Summary. In 14 insulin dependent diabetics past their initial remission period B-cell function was evaluated using a test meal before and after 1 week of strict blood glucose control, and again 3 weeks later when the patients were outpatients on conventional therapy. Eight patients with fasting C-peptide above 0.07 nmol/l improved their B-cell function significantly ($p < 0.05$) during the period of strict blood glucose control. However, the improvement was of short duration and was absent 3 weeks later in most patients. Six patients with fasting C-peptide below or equal to 0.07 nmol/l had no significant improvement in B-cell function during the period of strict control. The study shows that B-cell function and degree of blood glucose control are related in patients with fasting C-peptide above 0.07 nmol/l, and that B-cell function can change within days.

Key words: Glycaemic control, B-cell function, insulin-dependent diabetics, C-peptide, endogenous insulin secretion.

The onset of insulin-dependent diabetes mellitus is associated with B-cell failure [1, 2]. However, during the first months after onset most patients have increasing endogenous insulin secretion with a decreasing need for exogenous insulin [3–6]. It is now well established that even a low level of endogenous insulin secretion contributes to the quality of metabolic control in insulin-dependent diabetes mellitus (IDD) [3, 7–10].

Mirouze et al. [11] have shown that strict control by means of the artificial pancreas may lead to improvement in B-cell function in IDD of recent onset. However, there has been no study of whether good control of blood glucose contributes to the preservation or improvement of B-cell function in patients who have passed their initial remission.

We have therefore studied B-cell function before, during and 3 weeks after one week of strict blood glucose control in IDD patients with more than 6 months duration of disease.

Material and Methods

Patients

Fourteen patients were selected from among outpatients either because of known presence of residual B-cell function or because their clinical course suggested the presence of some residual B-cell function. Informed consent was obtained from each patient before hospitalisation. All were considered insulin-dependent at diagnosis because of at least 5% glucosuria, significant ketonuria (at least ++ with Ketostix) and body weight below 110% of the ideal weight [12]. At the time of the study none had acute illness or were taking medication other than insulin. On admission to hospital standard bicarbonate in plasma was within the normal range. Clinical characteristics are shown in Table 1.

Table 1. Individual clinical data in 14 insulin-dependent diabetics studied

Patient	Sex	Age (years)	Duration of diabetes (months)
1	♀	19	12
2	♀	33	7
3	♂	30	45
4	♂	17	10
5	♀	32	22
6	♀	22	15
7	♂	27	26
8	♀	37	26
9	♂	26	18
10	♀	34	13
11	♀	22	13
12	♀	31	177
13	♂	16	27
14	♀	38	15

0012-186X/81/0020/0530/$01.00

Table 2. Insulin dose and measures of the glycaemic response, in the 14 patients studied. Insulin dose: Period I, daily dose before admission to hospital; period II, average daily dose from the morning of day 2 to the morning of day 8; period III, daily dose from discharge to test III. Mean blood glucose was calculated from the morning of day 2 to the morning of day 8 using 9 values/24 h. M-value was calculated for the same 6 days using 6 blood glucose values/24 h. Glucosuria/24 h is from the last 24 h before each meal test. [a] = ketonuria detected with Ketostix

Patient	Insulin dose U/kg/24 h			Mean blood glucose		Glucosuria g/24 h		
	Period I	Period II	Period III	mmol/l	M-value	Test I	Test II	Test III
1	0.47	0.87	0.47	6.7	19.2	103[a]	12	0
2	0.47	0.56	0.47	7.8	22.0	87	9	5
3	0.46	0.81	0.46	6.8	12.1	75	0	54
4	0.33	1.41	0.46	7.8	18.3	200[a]	0	201[a]
5	0.33	0.77	0.33	4.9	20.9	73	0	48
6	0.34	0.59	0.34	7.0	12.9	128[a]	5	
7	0.38	0.58	0.38	4.9	13.7	27	0	2
8	0.40	1.22	0.40	6.7	22.9	53	0	35
9	0.34	0.74	0.34	7.2	9.7	45	0	6
10	0.55	0.76	0.66	6.8	12.5	83	0	47
11	0.55	0.95	0.55	7.1	23.2	30	2	0
12	0.44	0.76	0.59	6.9	17.1	94	0	60
13	0.66	1.37	0.69	7.0	12.8	85[a]	0	114[a]
14	0.91	0.96	0.91	6.7	15.3	5	0	21

Methods

Patients were studies for 28 days. They were admitted fasting to the hospital the morning of day 1 when meal test I was carried out. From day 1 to day 8 the patients were given 9 injections a day of a short acting insulin (Actrapid), aiming at normoglycaemia. Dosage was adjusted according to preinjection blood glucose measurements (Reflotest) and by the blood glucose response to the previous days insulin dose. Insulin was given IM preprandially and SC between meals. The times and average fractional doses of insulin were 0730 h 22.9 ± 0.8% (mean ± SEM), 0930 h 2.7 ± 0.5%, 1115 h 17.5 ± 0.6%, 1400 h 11.5 ± 0.6%, 1700 h 16.7 ± 0.7%, 2000 h 9.9 ± 0.5%, 2300 h 6.8 ± 0.4%, 0200 h 6.0 ± 0.4% and 0500 h 6.0 ± 0.4%. Meal test II was carried out the morning of day 8 after the patients had taken the pre-study morning dose of insulin. Thereafter the patients continued with their pre-study insulin regime and were discharged after a few days (maximum 3 days), except for 4 patients who were discharged with increased daily dose of insulin. The patients were seen on day 28 where meal test III was carried out. One of the patients (number 6) only participated in test I and II.

During the study period, the patients received a standard isocaloric diet, of which 20, 30 and 35% of the total caloric intake was given at breakfast, lunch and dinner respectively, the rest divided equally into three snacks at 0930 h, 1500 h and 2100 h.

B-cell function was evaluated using a test meal of 490 calories (60% carbohydrate, 26% fat and 14% protein). At test I, II and III the patients, except the four who were discharged with greater daily dose of insulin, injected their pre-study morning insulin dose 10 min before starting eating. Blood samples were taken −10, 0, 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min after starting to eat. The meal was completed in 10 min.

B-cell function was assessed by calculating the amount of insulin secreted following the test meal from the total area under the plasma C-peptide curve from 0–180 min and assuming a metabolic clearance rate of 310 ml/min [13]. To compensate for the different blood glucose levels the insulinogenic index was calculated by dividing the area below the C-peptide concentration curve (0–180 min) by the area under the glucose concentration curve (0–180 min). The sensitivity of the B-cell to glucose changes during meal tests was assessed by calculating the slope of the individual regression lines ($y = ax + b$) between C-peptide and blood glucose.

Blood glucose was measured by a glucose-oxidase method [14]. C-peptide concentrations (CPR) were measured by the method of Heding [15] employing the antiserum M1230 [16, 17]. The within and between assay coefficients of variation were 3.2 and 9.6%, respectively [16]. Patients with a plasma CPR level exceeding the upper range of CPR levels measured in 10 pancreatectomised patients (0.05 nmol/l) were considered to have residual insulin secretion [16]. The cross-reactivity with human proinsulin is very low with antibody M 1230. Thus, the proinsulin concentration has to exceed normal fasting level with a factor of more than 200 before any proinsulin is detected as CPR [17].

All samples from one subject were analysed in the same assay.

Blood glucose control was assessed by calculating mean blood glucose (9 values/24 h) and M-value (6 values/24 h) [18].

Hendriksen et al. [19] have previously shown that fasting C-peptide concentration above 0.07 nmol/l constitutes metabolically important insulin reserve. Therefore, the patients were divided into two groups according to whether initial fasting C-peptide concentration was above (numbers 1–8) 0.07 nmol/l or equal to or below (numbers 9–14) this value.

For statistical evaluation the Mann-Whitney rank sum test or Wilcoxon's test were used for comparison of mean concentrations. Type 1 error (2 α) was set at 0.05.

Results

The individual mean blood glucose and M-values are shown in Table 2. Eight patients (numbers 1–8) had fasting CPR above 0.07 nmol/l initially (range 0.09–0.21 nmol/l) (group I), while 6 patients (numbers 9–14) had CPR equal to or below 0.07 nmol/l (group II). During the period of strict blood glucose

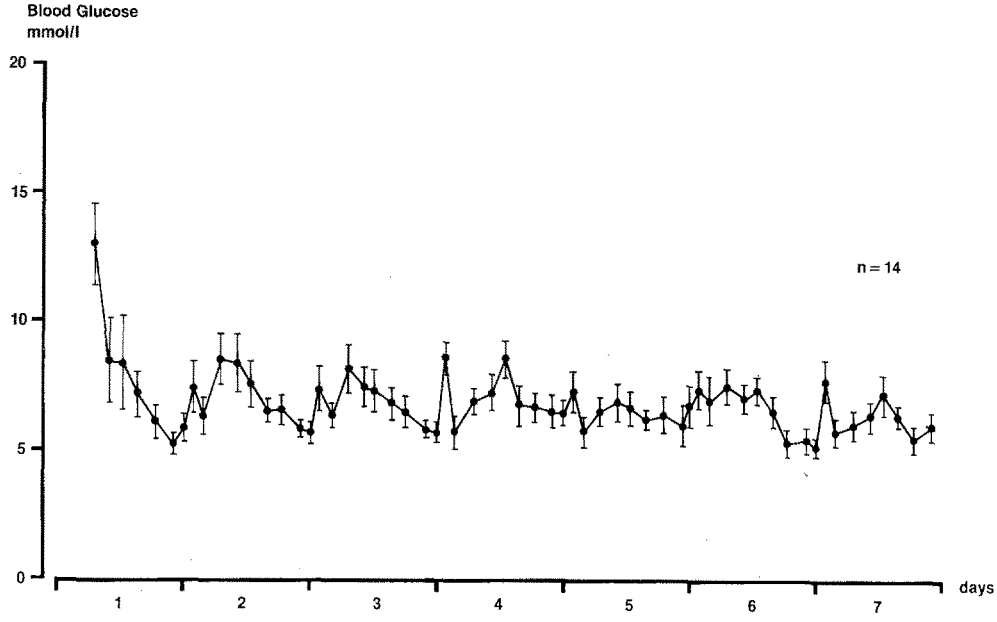

Fig. 1. Blood glucose concentrations during one week of strict glycaemic control (n = 14). Results are mean ± SEM

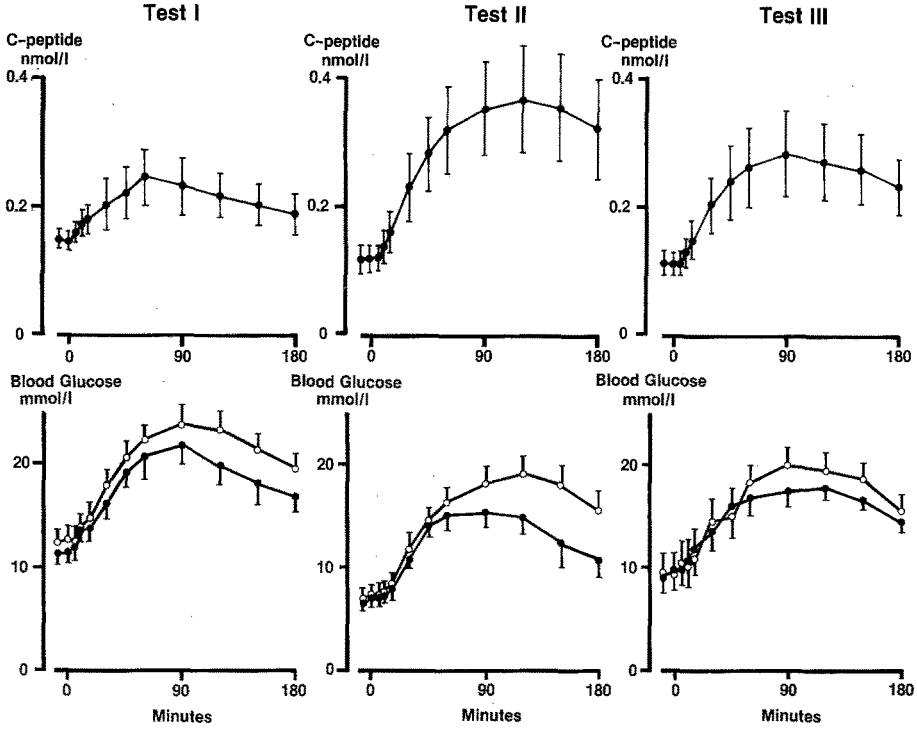

Fig. 2. C-peptide and blood glucose concentrations during meal tests I, II and III. Mean ± SEM. •—• group I (fasting CPR > 0.07 nmol/l); ○—○ group II (fasting CPR < 0.07). For the last group only blood glood glucose concentrations are illustrated

control no difference was found between the two groups in the quality of control. The average diurnal blood glucose profile is shown in Figure 1. In both groups strict glycaemic control was obtained with an average mean insulin dose of 54 U/24 h, range 41–88 U/24 h.

In group I after one week of strict blood glucose control the average amount of insulin secreted had increased 44% (range −31% to 135%, $p < 0.05$) at test II (Fig. 2) despite a smaller glycaemic stimulas as evaluated from the area under the blood glucose curve (mean − 30%, range + 6% to − 54%, $p < 0.05$). Only one of the patients (number 3), with a 54% decline in glycaemic stimulus, failed to show an increase in the amount of insulin secreted. All 8 patients in group I showed improved insulinogenic

Table 3. Insulinogenic index and B-cell sensitivity at test I, II and III in group I patients. The insulinogenic index was calculated using the area below the C-peptide concentration curve and the blood glucose concentration curve from 0–180 min. The B-cell sensitivity was calculated as the slope of the individual linear regression line using all the C-peptide and blood glucose values from −10 to 180 minutes

			Test I	Test II	Test III
			⊢——P < 0.01——⊣		
Insulinogenic index	$\left(\frac{\text{area cp}}{\text{area BG}} \times 10^3\right)$	mean	13.3	24.4	16.7
		range	4.1–40.4	5.6–48.4	5.8–39
			⊢——————————P < 0.01——⊣		
			⊢——P < 0.01——⊣		
B-cell sensitivity	$\frac{\text{nmol cp}}{\text{mmol BG}}$	mean	0.012	0.026	0.021
		range	0.001–0.059	0.004–0.062	0.003–0.062

indices ($p < 0.01$) and B-cell sensitivity ($p < 0.01$) at test II compared with test I at admission (Table 3).

After 3 weeks as outpatients the amount of insulin secreted in group I was still improved in 5 patients ($p > 0.05$) compared with test I. The glycaemic stimulus was not different between tests I and III. The insulinogenic index was also the same as at admission (Table 3), although B-cell sensitivity (Table 3) was still improved in all patients ($p < 0.01$). Compared with test II all patients except two secreted less insulin ($p > 0.05$) and in all but 2 patients insulinogenic index ($p > 0.05$) and B-cell sinsitivity ($p > 0.05$) had also declined at test III (Fig. 2, Table 3).

In group II 3 patients (no. 12, 13 and 14) did not show any measureable C-peptide at any of the three tests. Patient 10 had detectable CPR (0.06 nmol/l) at a few time points with blood glucose values above 18.6 mmol/l. Patient 11, who showed no B-cell function at admission demonstrated a definite but small B-cell response at a few sample points in test II (maximum CPR 0.08 nmol/l). This response was preserved 3 weeks later (maximum CPR 0.08 nmol/l). Patient 9 showed a small CPR response at all tests for blood glucose values above 10.2 mmol/l, without any significant changes during the study (maximum CPR 0.12 nmol/l).

Numerically the area under the blood glucose curves on average were 12%, 21% and 7% greater in group II compared with group I at test I, II and III, respectively ($p > 0.05$, Fig. 2). On admission to hospital (Table 2) group II was on average treated with 44% greater daily dose of insulin ($p < 0.05$) than group I.

Discussion

The results demonstrate that one week in a metabolic ward with strict blood glucose control can cause an improvement in endogenous insulin response in IDD. This is probably an effect of the better control but changes in diet, sympathetic tone and other factors may have contributed. Hendriksen et al. [19] and Gonen et al. [9] have suggested that a fasting CPR above 0.07 to 0.10 nmol/l indicates metabolically important insulin reserve. The present results imply that the same C-peptide concentration is the value above which an improvement in B-cell function may be expected from an improvement in glycaemic control.

During the period of strict blood glucose control similar control was obtained in the two groups in contrast to earlier findings of better control in patients with some insulin secretory reserve [3, 8, 9]. In the present study strict glycaemic control was obtained with an insulin dose 95% greater than the pre-study dose. This higher insulin dose together with the lower average 24 h blood glucose concentration may suppress endogenous insulin secretion [11, 20] so much that its metabolic effect becomes less pronounced. This lower secretory activity may explain the higher B-cell response after the period of strict control. Thus, when stimulated in this situation, larger stores of insulin ready for secretion may have been accumulated in the B-cells. Further studies are however needed to elucidate the mechanism of the recovery of B-cell secretory capacity after strict control.

After 3 weeks as outpatients on conventional insulin therapy the B-cell sensitivity was improved in all group I patients and the amount of insulin secreted was improved in 5 patients compared with test I. This may be a direct effect of the intensified insulin treatment, or an indirect effect of the whole study in that the patients observed the instructions given to a greater extent and thus maintained a better degree of control compared to the pre-study period. Compared to test II all patients except two secreted less insulin after 3 weeks as outpatients. Therefore the results suggest that B-cell function in insulin-dependent patients is related to glycaemic control and that B-cell function may change within a week.

The results are complementary to those obtained by Mirouze et al. [11], who studied insulin-dependent patients of recent onset. Our results confirm that B-cell function may be improved even if the disease has lasted for years. Apparently this improvement is of short duration, unlike the results of Mirouze et al. [11]. The discrepancy between the duration of the improvement of the B-cells may be explained by the longer duration of disease in our patients. In non insulin-dependent diabetics Turner et al. [21] found that first-phase insulin response to intravenous glucose was improved after one night of normoglycaemia using an IV insulin infusion, whereas no improvement was found in the insulin response to breakfast.

The study has also shown that good blood glucose control, close to that seen using open loop insulin infusion systems [22, 23], can be obtained using frequent glucose measurements and frequent injections of soluble insulin.

Acknowledgement. We are indebted to Ms. Jane Falk for her technical assistance. This study was supported by a grant for the Danish Medical Research Council (No. 512–20136).

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Received: September 12, 1980,
and in revised form: December 4, 1980

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