Importance of Glucose Control for the Recovery from Hypoglycemia in Insulin-dependent Diabetics

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SUMMARY

To evaluate whether the delayed glucose compensation after hypoglycemia in insulin-dependent diabetics was associated with their elevated blood glucose levels, five diabetic patients were studied before and after a period of intensified metabolic control. The glucose recovery rate was found to be improved after better diabetic control. This influence seems to be better reflected by the mean diurnal level rather than the glucose level immediately before hypoglycemia. The improvement occurred despite the same or lower levels of the important glucocompensatory hormones. These results show the importance of antecedent metabolic control for glucose compensation after hypoglycemia. DIABETES *31*:771–775, September 1981.

Previous studies have shown that the recovery rate following hypoglycemia induced with an intravenous injection of insulin is delayed in type I (insulin-dependent) diabetics.[1,2] Further studies[3] have shown that this unexpected finding can in part be attributed to a delayed insulin clearance combined with an impaired glucagon release. Levels of the other important counterregulatory hormones, including catecholamines, were essentially normal during the hypoglycemia, indicating that they could not compensate for the lack of glucagon in the diabetic subjects.[3]

Hepatic glucose production and uptake is not only regulated by the glucocompensatory hormones but also to a large extent by the ambient glucose concentration (see the review in ref. 4). In agreement with this, the switch between glucose uptake and production in the liver seems to be impaired in both diabetic animals[5] and man.[6]

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The biochemical basis for the regulatory effect of glucose per se appears to be mainly exerted at the level of hepatic glycogen phosphorylase activity.[4] This key enzyme for hepatic glucose production becomes inactivated by elevated glucose levels.[4] Consequently, elevated glucose levels in diabetics may be important for their delayed recovery rate following hypoglycemia.

To test this hypothesis, type I diabetics were made normoglycemic on the morning before the induction of hypoglycemia. Furthermore, the same subjects were studied twice, before and after a period of intensified diabetic control.

PATIENTS AND METHODS

Patients. Five male, insulin-dependent diabetic subjects were studied. They were all considered to have stable diabetes and were recruited from the Diabetes Outpatient Clinic where they have been undergoing regular monitoring. Their age ranged from 21 to 48 yr (mean 32 yr) and duration of diabetes was from 6 to 25 yr (mean 10 yr). They were regularly treated with a combination of intermediate- and short-acting insulin (Monotard and Actrapid insulins, Novo, Denmark) taken subcutaneously twice daily. The patients took no medication other than insulin (for further clinical details see Table 1).

The presence of autonomic neuropathy was evaluated in the patients according to the methods of Ewing et al.[7] and Mackay et al.[8] One of the patients had evidence of autonomic neuropathy according to both tests, but without clinical symptoms.

Methods. The patients were hospitalized during the study period. Hypoglycemia was induced twice in each patient. Treatment with regular intermediate-acting insulin was exchanged for short-acting insulin (Actrapid, Novo) at least 38 h before the first hypoglycemia. During both treatment periods insulin was given three times a day about 30 min before each meal. The amount of insulin required was evaluated by continuous blood glucose determinations. The first hypoglycemia (I) was induced after 2 days in hospital under normal,

TABLE 1
Clinical characteristics

Patient no.	Age (yr)	Diabetes duration (yr)	Weight (kg)	Height (cm)	Ordinary insulin dose (IU/day)	Known diabetic complications
1	21	10	83	194	92	None
2	28	6	82	180	56	None
3	31	25	80	184	68	None
4	31	5	67	175	42	None
5	48	6	89	180	38	Autonomic neuropathy,* mild proteinuria (<0.3 g/day)

* See METHODS for details.

but not rigorous blood glucose control. The patients received a slow intravenous infusion of insulin the night before the study. The second hypoglycemia (II) was induced 3 days later after a period of intensified control. In both studies blood glucose was kept under control during the night with a slow, continuous, intravenous infusion of insulin. The aim was to reach normoglycemia in the morning before the induction of hypoglycemia. The i.v. infusion was terminated just before the bolus dose was given (see below). Blood glucose levels had then been stable for at least 1 h. The last s.c. dose of short-acting insulin was given 16 h before hypoglycemia.

Four of the patients required, on the average, 26% more insulin during the period of improved control compared with their regular insulin dose. One of the patients, who normally had a high dose of insulin (92 IU/day), required 6% less.

Blood glucose was controlled with a reflectometer (Reflomat, Clinicon International GMBH, West Germany) before and after each meal, 8 times during the day, and 3 times during the night. As an estimate of diurnal blood glucose control M-values were calculated using the formula of Schlichtkrull et al.[9] as modified by Service et al.[10]

After a diet history all patients were placed on a 2500-kcal/day diabetic diet (10,480 kJ).

Hypoglycemia was induced by i.v. insulin given rapidly. The same i.v. bolus dose of insulin was given on both occasions (0.18 ± 0.01 IU/kg, mean ± SEM). However, three of the patients received an additional 4 IU insulin i.v. during the second hypoglycemia (after improved control) to become hypoglycemic. After insulin injection blood glucose levels were followed every 5 min with the reflectometer to catch the glucose nadir. Blood samples were drawn in an antecubital vein at the indicated times following the nadir. The blood glucose levels shown were determined with the glucose-oxidase technique (Kabi AB, Stockholm, Sweden).

Catecholamines were determined with an isotope technique,[11] cortisol with a fluorimetric method, and growth hormone with a double-antibody technique (kindly performed by Prof. G. Lindstedt, Department of Clinical Chemistry, Sahlgren's Hospital, Gothenburg). Plasma glucagon was assayed with antiserum E7.[12] This antiserum, which recognizes the carboxy-terminal region of glucagon, has been characterized with antiserum 30K as reference.[13] Total insulin was determined with a radioimmunoassay (Phadebas, Pharmacia, Uppsala, Sweden) and free insulin after precipitation of insulin antibodies with polyethylene glycol according to Kuzuya et al.[14]

The significance of differences between the two studies was analyzed with Student's paired *t* test. The values shown are means ± SEM unless otherwise indicated.

RESULTS

GLUCOSE LEVELS

The mean diurnal blood glucose level the day before the first hypoglycemia (I: 8.4 ± 0.6 mmol/L, mean ± SEM) was significantly higher than that on the day before the second (II: 6.2 ± 0.9 mmol/L, $P < 0.005$). M-values the day before the first hypoglycemia were also higher in all patients than those on the day before the second hypoglycemia (Table 2).

Blood glucose levels 4 h before hypoglycemia (at 4:00 a.m.) were higher on the morning of the first hypoglycemia (8.0 ± 0.9 mmol/L) as compared with the second (5.4 ± 0.7 mmol/L). However, blood glucose levels on the morning immediately before the induction of hypoglycemia were not significantly different between the two studies (I: 5.4 ± 0.9; II: 4.6 ± 1.1 mmol/L).

After insulin injection blood glucose levels decreased to nadir values after 60–90 min. Glucose nadir occurred somewhat later during the second hypoglycemia, since three patients required an additional injection of 4 IU insulin to become hypoglycemic. Nadir glucose values were similar (Figure 1) on both occasions (I: 0.8 ± 0.1 mmol/L, II: 1.2 ± 0.2 mmol/L; $P > 0.05$).

After nadir the initial rate of glucose recovery was slow in these subjects, considerably slower than in nondiabetic subjects, but similar to that previously found.[3] No clear initial, rapid phase of increase was seen on either occasion

TABLE 2
M-values in the diabetics the day before the first (I) and second (II) hypoglycemia

Patient no.	M-values I	M-values II
1	22	8
2	22	17
3	34	6
4	100	23
5	31	15

M-values according to Service et al. $M = \frac{\Sigma\left[10 \times \log \frac{BG}{4.44}\right]^3}{N}$

where BG = blood glucose levels; N = number of observations.

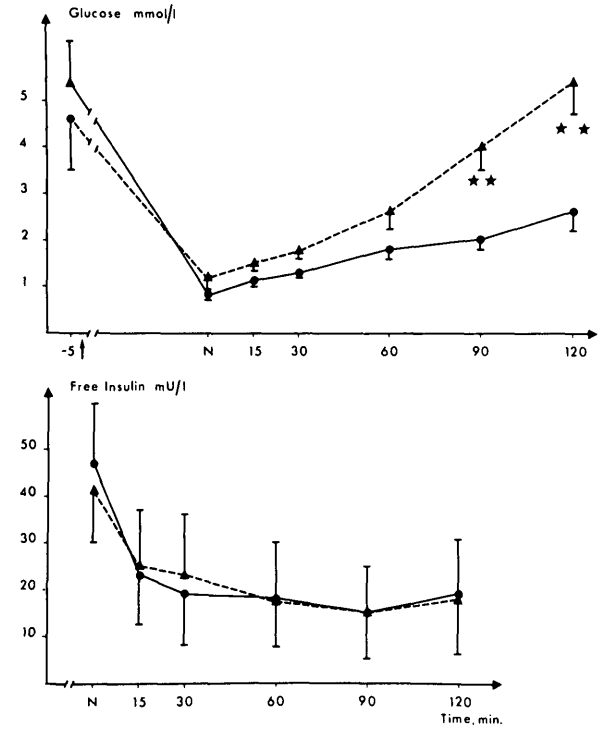

FIGURE 1. (Top). Blood glucose levels during insulin-induced hypoglycemia before (●—●) and after (▲---▲) a period of improved diabetic control. N = 5. **P < 0.025. Arrow, insulin injection. (Bottom) Blood levels of free insulin in the same patients. N, glucose nadir. Values shown are means ± SEM.

(Figure 1). However, from about 30 min and onwards the glucose increase was considerably more rapid during the second hypoglycemia. After 120 min the initial glucose levels had been reached following the second but not the first hypoglycemia (5.4 ± 0.7 and 2.6 ± 1.4 mmol/L, respectively, $P < 0.025$). The glucose recovery rate in the patient with neuropathy was similar to that of the patients without evident neuropathy during the first hypoglycemia. Improved glucose compensation was also found in this patient after the period of better diabetic control.

One of the patients (no. 4) had a considerably higher M-value the day before the first as compared with the second hypoglycemia (100 versus 23, Table 2). Glucose nadir levels were equal in this patient at the two hypoglycemic episodes (1.1 mmol/L). However, the glucose recovery rate was much improved during the second hypoglycemia and an initial, rapid phase was also seen (Figure 2).

INSULIN LEVELS

Plasma levels of both total and free insulin were similar at glucose nadir (free insulin I: 47 ± 13 mU/L; II: 41 ± 17 mU/L, $P > 0.05$) and thereafter in the two studies (Figure 1).

COUNTERREGULATORY HORMONES

Catecholamines. Fasting adrenaline levels were somewhat higher in the first study compared with the second (0.50 ± 0.09 and 0.30 ± 0.05 nmol/L, respectively). Also, at glucose nadir the increase tended to be higher in the first study ($0.05 < P < 0.1$) (Figure 3A). Plasma noradrenaline levels increased in both studies and this increase was also somewhat less in the second study (data not shown).

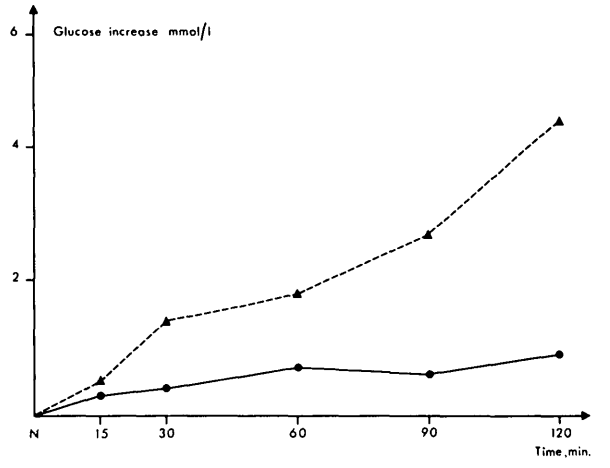

FIGURE 2. Blood glucose recovery in a diabetic patient before (●—●) and after (▲----▲) the improved control. N, glucose nadir.

Glucagon. Some increase in plasma glucagon was found in both studies during hypoglycemia (Figure 3B). Glucagon levels tended to be higher during the first study but statistical significance was only achieved at 15 and 60 min after the glucose nadir.

Cortisol. Fasting cortisol levels were similar in the two studies (528 ± 59 and 518 ± 42 nmol/L, respectively). Maximal cortisol values were reached somewhat later than the peak glucagon levels in both studies. There was no significant difference between the peak cortisol levels reached during the two hypoglycemic episodes (Figure 3C). However, the levels remained elevated during the first hypoglycemia.

Growth hormone. Significantly higher fasting growth hormone levels were found in the first study compared with the second (14 ± 4.4 and 2.6 ± 0.3 mU/L, respectively, $P < 0.025$). During hypoglycemia similar peak growth hormone levels were reached, but this occurred somewhat later in the first study (Figure 3D). Growth hormone levels also remained elevated for a longer period of time during the first hypoglycemia.

DISCUSSION

The present study shows that the slow spontaneous rate of glucose recovery previously reported in insulin-dependent diabetics[1-3] is not due to their elevated glucose levels at the time of the study. In the present investigation normoglycemia was essentially achieved in the mornings before the induction of hypoglycemia. Furthermore, it was found that glucose recovery could be greatly increased in the same subjects after a period of improved diabetic control. Intermediate-acting insulin was withdrawn for at least 38 h and the patients were treated with only short-acting insulin in connection with meals and i.v. insulin overnight. Consequently, the slow spontaneous glucose recovery in the diabetics previously reported[1-3] cannot be due to any possible remaining insulin in the subcutaneous depot.[15]

Glucose levels were not measured the day before the patients arrived at the hospital. However, since insulin was then only given twice daily, high postprandial glucose levels probably occurred. Even before the first study the glucose control achieved with three doses of short-acting insulin before each meal and an insulin infusion during the

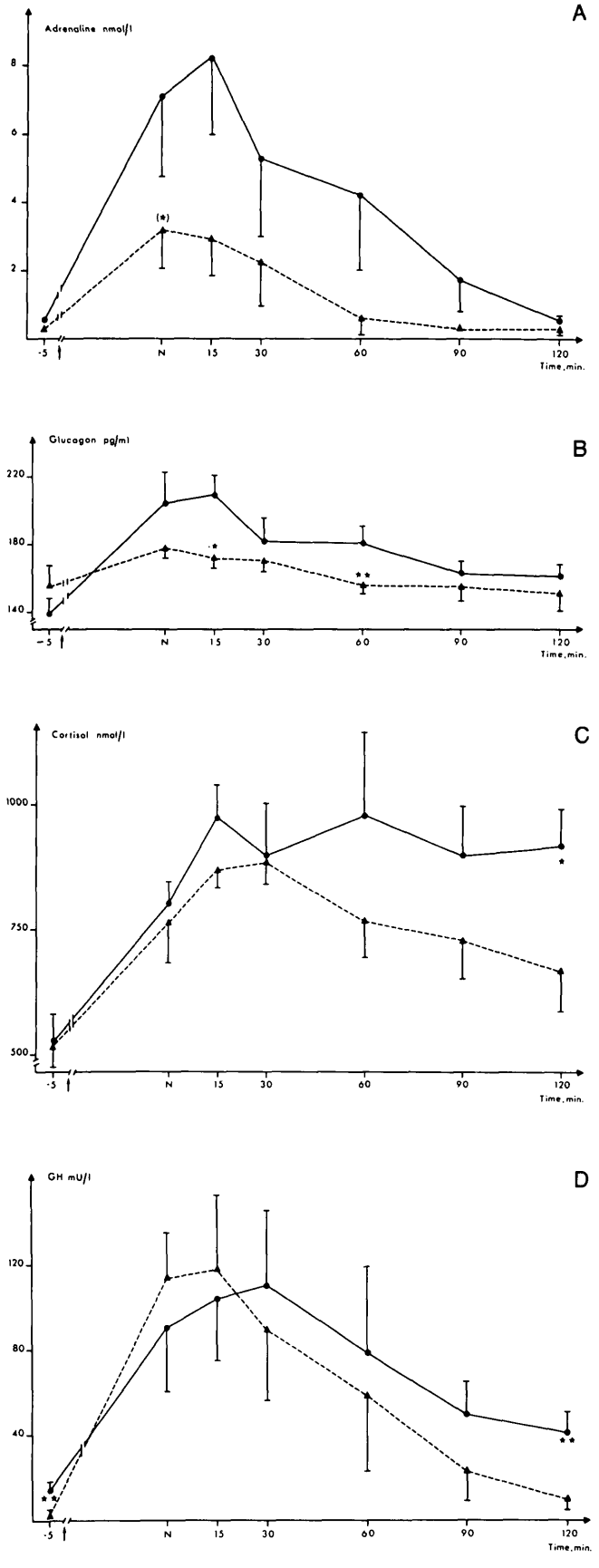

FIGURE 3A–D. Counterregulatory hormones during insulin-induced hypoglycemia before (●—●) and after (▲----▲) improved diabetic control. (*)0.05 < P < 0.01, *P < 0.05, **P < 0.025. Arrow, insulin injection. N, nadir. Values shown are means ± SEM.

night before the study was probably better than that during the patients' regular insulin regimen. A further improvement was achieved during the second part of the study. The lower fasting growth hormone levels are probably a sign of better blood glucose control.[16–18]

The finding of an increased rate of glucose recovery following improved diabetic control could be due to different levels of circulating insulin and/or counterregulatory hormones. However, the plasma levels of both total and free insulin were similar at glucose nadir and throughout the period of glucose compensation on both occasions. Furthermore, peak levels of all counterregulatory hormones were either similar or higher during the first hypoglycemia, which, in turn, was associated with a slower rate of recovery. The somewhat higher and prolonged elevation of the important counterregulatory hormones during the first study was probably mainly accounted for by the more prolonged hypoglycemia. Thus, despite similar circulating insulin levels, similar or even increased levels of catecholamines and glucagon, and similar cortisol and growth hormone peaks during the first hypoglycemia, the glucose recovery rate was delayed compared with the second study. This, in turn, implies that the improved recovery rate was due to the better glucose control during the second study or to some factors associated with the glucose control.

Several studies have shown that glucose concentration per se is important for glucose production in the liver independent of the glucocompensatory hormones.[19,20] Elevated glucose levels have been found to reduce hepatic glucogenolysis by probably glycosylating and thereby reducing the activity of the key glycogenolytic enzyme glycogen phosphorylase.[21] Liver glycogenolysis is also decreased in favor of increased glycogen synthesis at high glucose levels since glucose inhibits glucose-6-phosphatase activity.[22] Also, gluconeogenesis appears to be influenced by the ambient glucose concentration,[23] although the biochemical mechanisms for this have been less well defined.

The present findings, then, are consistent with the hypothesis that a period of improved glucose control resulted in increased activity of the key liver enzymes, with increased glucose production as a consequence. Whether this is due to an increased hormonal responsiveness by enzymes (and then probably the catecholamines mainly) or due to an increased sensitivity of the autoregulation of hepatic glucose production remains to be established.

The initial, rapid phase of glucose recovery regularly seen in healthy subjects[3,24] was only partially seen during the second hypoglycemia. A longer period of rigorous blood glucose control could possibly have also normalized the initial, rapid phase of glucose recovery.

Finally, the alleged effect of the previous degree of diabetic control of the key glucogenic enzymes may not only be important for the rate of glucose recovery. It may be equally important in normalizing hepatic sensitivity to adjust glucose production according to the ambient glucose level.

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