Pathogenesis and Prevention of the Dawn Phenomenon in Diabetic Patients Treated with CSII

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SUMMARY

The mechanism of the dawn phenomenon was studied in 12 C-peptide-negative type I diabetic patients (age 30 ± 2 yr) treated with continuous subcutaneous insulin infusion. During constant basal infusion, nocturnal glycemia remained constant until 4 a.m., but began to rise thereafter in 10/12 patients, with the mean rise from 4.6 ± 0.4 mmol/L to 6.1 ± 0.7 mmol/L ($P < 0.01$) by 8 a.m. In these patients the rate of glucose production (R_a, 2.14 ± 0.04 mg/kg/min, 3-H^3-glucose infusion) exceeded the rate of utilization (R_d, 1.89 ± 0.03 mg/kg/min, $P < 0.02$). When the patients were restudied after the infusion rate was increased by 49 ± 7%, R_a fell to 1.75 ± 0.03 mg/kg/min ($P < 0.01$) and the dawn phenomenon was abolished. However, both R_a and R_d remained higher in the diabetic subjects ($P < 0.05$) than in eight healthy control subjects, in whom R_a (1.66 ± 0.02 mg/kg/min) was equal to R_d with glycemia remaining unchanged. Peripheral free insulin levels in the diabetic patients were similar during constant (12.3 ± 0.5 mU/L) and increased infusion rate (11.3 ± 0.4 mU/L), and higher than those of the control subjects (5.2 ± 0.2 mU/L, $P < 0.05$). A diurnal rise in serum cortisol levels occurred 1 h earlier in the diabetic than in the control subjects, and R_a was directly proportional to serum cortisol concentration ($r = 0.61$; $P < 0.01$). Serum growth hormone levels were also slightly higher in the diabetic than the control subjects.

In conclusion: (1) A dawn phenomenon is associated with an excessive rate of glucose production, rather than impaired utilization; (2) this may be explained, at least in part, by elevated counterregulatory hormone levels; and (3) a step-up in the overnight insulin delivery reduces hepatic glucose production and so prevents the dawn phenomenon. DIABETES 1986; 35:78–82.

Although an early morning rise in blood glucose in diabetic patients (the dawn phenomenon) has long been recognized, its etiology and pathogenesis remain unknown. A reactive, posthypoglycemic hyperglycemia (Somogyi effect) was considered to be of importance already in the late 1930s.[1] More recently, Gale and co-workers demonstrated a close inverse correlation between the early morning rise in blood glucose and plasma insulin levels in insulin-treated patients,[2] suggesting that hypoinsulinemia may contribute to the rise in glycemia. In addition, a diurnal rise in counterregulatory hormones during early morning has been claimed to play a role in the pathogenesis of the dawn phenomenon.[3,4] The relative contribution of each of these factors (reactive hyperglycemia, hypoinsulinemia, and diurnal rise in counterregulatory hormones) to the pathogenesis of the dawn phenomenon is unknown. Moreover, whether the rise in glycemia is due to augmented glucose production or reduced uptake, or both, is unclear.

When the continuous insulin infusion rate is increased during the night, the rise in blood glucose can be reduced or abolished completely.[5] What the influence of enhanced insulin delivery is on counterregulatory hormone profiles, and whether it acts in suppressing glucose production, enhancing its peripheral uptake, or both, has not been studied during the phenomenon period. Consequently, the present study was planned to evaluate glucose kinetics during the early morning in patients treated with continuous subcutaneous insulin infusion by employing either constant or increased rate of insulin delivery.

MATERIALS AND METHODS

SUBJECTS

Twelve insulin-dependent diabetic patients [11 men, 1 woman; age 30 ± 2 yr; relative body weight 104 ± 3% (73 ± 2 kg/178 ± 2 cm), Metropolitan Life Insurance Tables, 1959] were studied. The mean duration of diabetes was 11 ± 2 yr. Their basal C-peptide levels were 0.10 ± 0.02 g/L (0.03 ± 0.01 nmol/L) with no increase after 1 mg intravenous glucagon stimulus. They all had been treated with con-

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tinuous subcutaneous insulin (Actrapid, Novo A/S, Copenhagen, Denmark) infusion with a portable pump (model AS6C, Auto-Syringe, Inc., Hooksett, New Hampshire, or Nordisk Infuser, Gentofte, Denmark) at least 1 mo before the study. The daily dose of insulin was 38 ± 3 U, of this 18 ± 2 U (47%) was administered as a basal infusion and the rest as boluses before meals. All subjects were in good control, as demonstrated by an HbA_1 of 8.9 ± 0.3% (normal range 6–9%). Two patients had mild background retinopathy, whereas no subject had any evidence of diabetic neuro- or nephropathy. Eight healthy males, matched for age (28 ± 1 yr) and relative body weight [106 ± 3%, (76 ± 2 kg/179 ± 2 cm)] served as controls. The purpose, nature, and potential risks of the study were explained to all subjects before consent to participate was obtained. The experimental protocol was approved by the Ethical Committee of the Helsinki University Hospital.

EXPERIMENTAL DESIGN

Each patient was studied at the metabolic ward of Helsinki University Hospital. On the day preceding the overnight study, the patients had their usual diet, containing 30 kcal/kg, with 50% carbohydrate, 30–35% fat, and 15–20% protein. The evening snack and insulin bolus were reduced by 50% and were taken 2 h earlier than usual, at 7:30 p.m. The mean evening bolus was 1.0 ± 0.1 U. Blood glucose was measured thereafter at 1–2-h intervals until midnight, and it varied between 4 and 10 mmol/L.

The first study was performed with the use of a constant basal infusion rate (0.75 ± 0.08 U/h). Since there are no generally accepted quantitative definitions for the dawn phenomenon, we used as a criterion a rise in blood glucose at least two times greater than that in healthy subjects, or ≥0.6 mmol/L. With this definition, 10 of 12 patients demonstrated a dawn phenomenon during constant basal infusion. These 10 patients were restudied and the basal infusion rate was raised overnight. The infusion pump was changed to a programmable Auto-Syringe 6 MP. The basal infusion rate was increased during the night on an individual basis based on the rise in blood glucose observed in the first study and on the nocturnal self-monitoring of blood glucose. In six patients, the basal infusion rate (0.70 ± 0.09 U/h) was raised by 65% (to 1.16 ± 0.12 U/h) in one step, an average of 40 min before midnight. In the other four cases the infusion rate (0.75 ± 0.12 U/h) was increased in two steps: first by 28% 30 min before midnight and by another 17% (to 1.12 ± 0.19 U/h) at 3 a.m.

There was at least a 1-wk interval separating the two studies. The control subjects were studied only once.

MEASUREMENTS

Endogenous glucose production. In both studies, an indwelling catheter was inserted at midnight in an antecubital vein for blood sampling, and it was kept patent with saline infusion. A second catheter was inserted in a forearm vein for the infusion of tritiated glucose. The glucose pool was labeled with a primed continuous infusion of D3-(^{3}H)-glucose (SA 5 Ci/mmol, Amersham, Buckinghamshire, England). The priming dose was given as a bolus injection of 25 μCi followed by a continuous infusion of 0.25 μCi/min. Following a 90-min equilibration period at 2 a.m., plasma samples for the determination of blood glucose (Beckman Glucose Analyzer IV, Beckman Instruments, Fullerton, California) and glucose specific activity were taken at 10-min intervals for 60 min, and at 20-min intervals thereafter until 8 a.m. D3-(^{3}H)-glucose activity was determined after deproteinization with $Ba(OH)_2$-$ZnSO_4$ and evaporation of ^3H_2O, as described.[6] The rate of hepatic glucose production and utilization was calculated using Steele's equation[7] with a pool fraction of 0.65.[8]

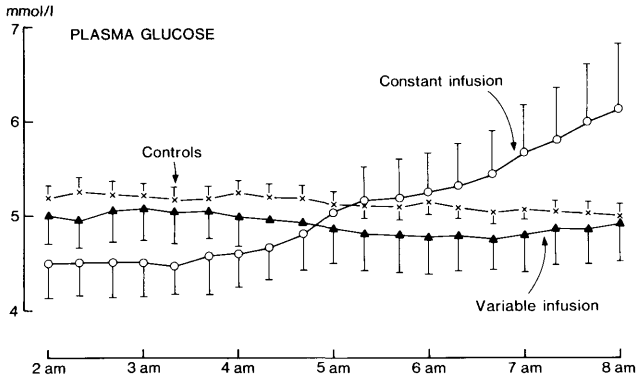

FIGURE 1. Changes in plasma glucose levels in healthy controls and in diabetic patients during continuous insulin infusion therapy with constant or step-wise increase of infusion rate.

Other measurements. From 2 to 8 a.m. samples were taken at 1-h intervals for the determination of plasma free insulin after precipitation with polyethylene glycol,[9] serum cortisol,[10] growth hormone,[9] plasma glucagon in the diabetic patients,[11] serum free fatty acids (FFA),[12] and, in healthy subjects, C-peptide.[13] Hemoglobin A_1 was determined by microcolumn chromatography.[14]

Statistical analysis. Intragroup statistical comparisons were made with Student's paired *t*-test; intergroup comparisons used analysis of variance using BMDP computer programs 7D.[15] Results are presented as means ± SEM for the 10 patients with dawn phenomenon, whereas the results of the other 2 patients are given separately.

RESULTS

Glucose metabolism. In the beginning of the study, plasma glucose levels were comparable between the patients treated with constant (4.5 ± 0.4 mmol/L) or variable insulin infusion (5.0 ± 0.4 mmol/L), and the healthy control subjects (5.2 ± 0.2 mmol/L) (Figure 1). While on the constant rate infusion, the mean plasma glucose levels rose to 6.1 ± 0.7 mmol/L ($P < 0.02$). The range of the increase was 0.6–4.2 mmol/L. When the infusion rate was increased, plasma glucose levels remained constant through the night. In the healthy controls, nocturnal plasma glucose levels varied within 0.3 mmol (Figure 1). The rate of glucose production in the three groups is shown in Figure 2. When plasma glucose levels rose between 4 and 8 a.m. during constant infusion, the mean rate of glucose production (R_a) increased significantly (Figure 2).* When the mean R_a was calculated at the time plasma glucose levels rose (from 4 to 8 a.m.), it was 29% higher in the group with constant infusion (2.14 ± 0.04 mg/kg/min) than in the healthy controls (1.66 ± 0.02 mg/kg/min, Figure 3). When the delivery rate was increased, R_a declined significantly. The mean level from 4 to 8 a.m. fell to

*There was no significant correlation between the rise in R_a and plasma glucose, however.

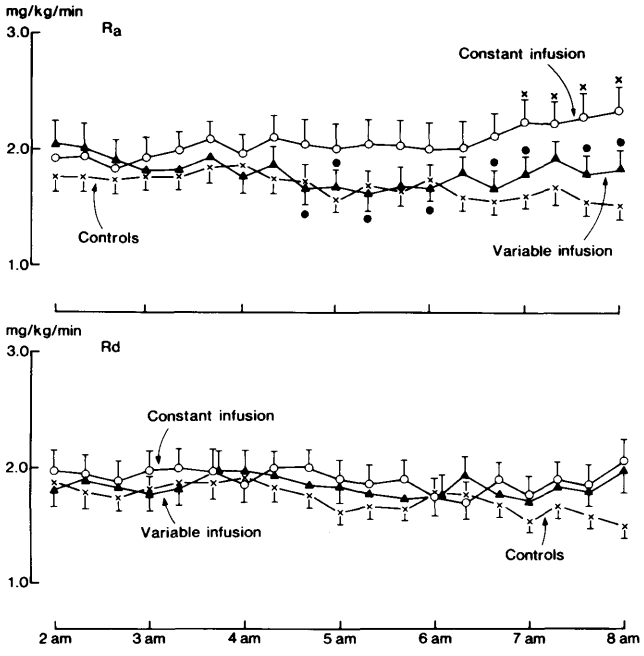

FIGURE 2. The rate of glucose production (R_a, upper panel) and glucose uptake (R_d, lower panel) in healthy controls and in diabetic patients during constant and step-wise increase of subcutaneous insulin infusion therapy. x = $P < 0.02$ versus the mean value before 4 a.m.; ● = $P < 0.05$ between constant and variable infusions.

1.75 ± 0.03 mg/kg/min, but still remained slightly above normal. The mean rate of glucose utilization (R_d) was comparable during constant and variable insulin delivery, and in both studies it was slightly (but significantly) above normal (Figures 2 and 3). The two patients who failed to demonstrate a dawn phenomenon had mean R_a values (1.67 ± 0.10 mg/kg/min and 1.73 ± 0.08 mg/kg/min) virtually identical to the control level. The values also matched well with the subjects' R_d's (1.59 ± 0.09 mg/kg/min and 1.71 ± 0.07 mg/kg/min, respectively). As a consequence, blood glucose values (3.3 and 4.2 mmol/L, respectively) in these patients remained unchanged.

Hormone response. Table 1 illustrates nocturnal hormone profiles of the three groups. In the diabetic patients, peripheral insulin levels were 2–3-fold above normal, and comparable regardless of whether insulin delivery remained constant or was increased during the night.

No nocturnal changes in free insulin levels were seen in any of the three groups. Also, C-peptide levels remained unchanged in the healthy controls (1.9 ± 0.3 μg/L versus 1.5 ± 0.1 μg/L at 2 and 8 a.m., respectively). In contrast, serum cortisol levels rose 3- to 4-fold in each group. In both diabetic groups, serum cortisol levels rose significantly at 4 a.m., which was 1 h earlier than in the healthy controls. At 8 a.m., the levels were significantly higher in the constant infusion group as compared with the patients treated with variable infusion. Serum cortisol at 8 a.m. was closely related to the rate of glucose production during the preceding 4 h in all three groups ($r = 0.61$, $P < 0.01$). Serum growth hormone levels were highest at 2 a.m. and thereafter fell gradually toward the morning. As compared with the control subjects, growth hormone was elevated in both diabetic groups at 4 a.m. and in the variable infusion group at 8 a.m. Baseline plasma glucagon levels during constant (221 ± 18 ng/L) and variable (211 ± 43 ng/L) insulin infusion were comparable and remained unchanged throughout the study.

In the two patients who failed to demonstrate a dawn phenomenon, the mean peripheral insulin levels (13.8 and 4.5 mU/L) were not higher, nor were cortisol (315 and 467 nmol/L) or growth hormone (1.0 and 10.0 μg/L) levels lower than the respective mean values in the other 10 patients (12.3 ± 0.5 mU/L, 317 ± 60 nmol/L, 3.7 ± 1.1 μg/L, respectively).

Free fatty acids. Serum FFA levels were similar in each group at the beginning of the study (Table 1). In the patients with constant insulin infusion, FFA levels rose at 8 a.m. and were higher than in the control subjects. In the other two groups, FFA levels remained unchanged through the night. The two patients without a dawn phenomenon did not differ from others regarding their mean FFA levels during the study (0.41 mmol/L, in both patients).

DISCUSSION

The dawn phenomenon is defined as a rise in plasma glucose and/or insulin requirements during early morning.[4,16] The prevalence of this phenomenon has varied from 0 to 88% in patients with type I diabetes.[3–5,16–18] The great variation can be explained, at least partly, by the lack of exact quantitative criterion for the dawn phenomenon; it also may depend on the patient population and the insulin therapy used. Inappropriately low insulin delivery rate overnight will lead to a rise in blood glucose, even in patients who would not have a dawn phenomenon with appropriate insulin regimens. In the current study, we used as a criterion a blood glucose rise at least twofold greater than in the healthy subjects. When this criterion was used, a dawn phenomenon occurred in 10/12 (83%) of our patients.

In the present study, the mean rate of glucose production in the patients treated with constant insulin infusion was 13% higher than the rate of glucose utilization, leading to a rise

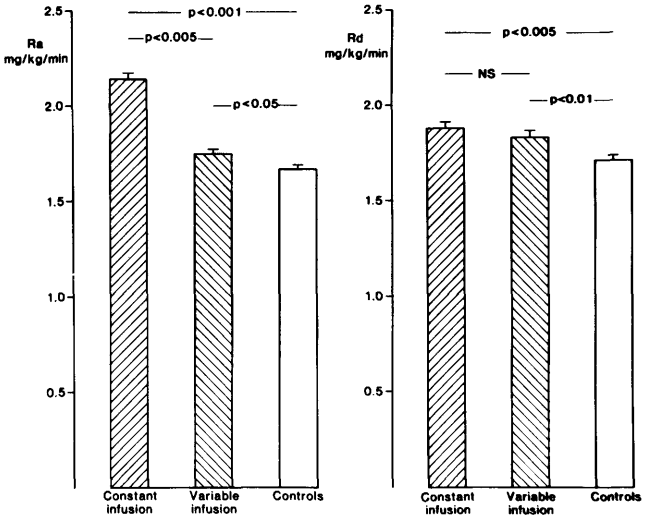

FIGURE 3. The mean rate of glucose production (R_a, left panel) and glucose uptake (R_d, right panel) between 4 and 8 a.m. in healthy controls and in diabetic patients treated with constant or step-wise increase of subcutaneous insulin infusion. The values are calculated from the data shown in Figure 2.

TABLE 1
Nocturnal hormone and free fatty acid (FFA) levels in healthy controls and in diabetic patients treated with constant (C) or variable (V) insulin infusions

			Time (a.m.)						
			2	3	4	5	6	7	8
Plasma free insulin (mU/L)	Diabetic	C	14.6 ± 4.4*	12.7 ± 3.7*	12.1 ± 3.2*	12.6 ± 3.9*	12.5 ± 4.2*	12.4 ± 4.0*	11.1 ± 3.6*
	Diabetic	V	10.9 ± 2.7*	9.8 ± 2.9*	10.6 ± 2.9*	11.7 ± 2.8*	10.9 ± 2.6*	12.9 ± 3.3*	12.1 ± 3.6*
	Control		5.2 ± 1.3	5.3 ± 1.6	5.4 ± 1.0	5.3 ± 1.1	5.9 ± 1.3	5.0 ± 0.9	4.0 ± 0.4
Serum cortisol (nmol/L)	Diabetic	C	120 ± 17	158 ± 38	216 ± 40†	355 ± 55†	372 ± 51†	443 ± 20†	558 ± 23†,‡
	Diabetic	V	114 ± 21	184 ± 59	232 ± 51†	346 ± 50†	353 ± 48†	432 ± 31†	430 ± 40†
	Control		115 ± 35	103 ± 25	107 ± 26	299 ± 60†	377 ± 26†	456 ± 27†	481 ± 18†
Serum growth hormone (μg/L)	Diabetic	C	7.6 ± 2.8	6.0 ± 1.6	6.6 ± 1.7*	2.3 ± 0.7	1.4 ± 0.3	1.5 ± 0.6	0.6 ± 0.2
	Diabetic	V	10.2 ± 3.8	6.1 ± 1.6	5.2 ± 1.0*	3.9 ± 2.1	5.0 ± 2.0	4.8 ± 1.8	1.5 ± 0.4*
	Control		4.8 ± 0.9	3.1 ± 1.4	1.6 ± 0.6	1.0 ± 0.2	0.6 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
Serum FFA (mmol/L)	Diabetic	C	0.42 ± 0.05	0.51 ± 0.06	0.41 ± 0.08	0.52 ± 0.10	0.41 ± 0.02	0.35 ± 0.03	0.68 ± 0.10*†
	Diabetic	V	0.42 ± 0.04	0.50 ± 0.04	0.38 ± 0.04	0.43 ± 0.05	0.39 ± 0.06	0.39 ± 0.05	0.50 ± 0.09
	Control		0.41 ± 0.07	0.51 ± 0.05	0.45 ± 0.08	0.47 ± 0.04	0.43 ± 0.03	0.37 ± 0.04	0.39 ± 0.06

*$P < 0.05$ versus control.
†$P < 0.05$ versus the value at 2 a.m.
‡$P < 0.01$ versus variable infusion.

in plasma glucose. However, no significant correlation existed between the rate of glucose production and the rise in plasma glucose. Thus, accelerated glucose production may not be the primary factor responsible for the rise in plasma glucose, but secondary to some other changes.

As compared with the healthy control subjects, glucose utilization was slightly higher in the diabetic patients, probably due to their peripheral hyperinsulinemia. Conversely, glucose uptake was still inappropriately low, since it did not keep pace with the rate of production. Elevated serum growth hormone and free fatty acid levels (perhaps due to hepatic hypoinsulinization) during constant insulin infusion may have prevented an adequate rise in the rate of glucose utilization.[19]

When the insulin infusion rate was increased, glucose production fell to match the rate of disposal, and plasma glucose levels remained unchanged. However, both the rate of production and utilization stayed above normal, indicating enhanced glucose kinetics in the face of normoglycemia.

Possible mechanisms of excessive glucose production, preceding hypoglycemia, are (1) a diurnal rise in counterregulatory hormones reduced insulin availability in portal circulation, (2) decreased insulin sensitivity,[20] or (3) any combination of these. A reactive counterregulation is an unlikely explanation, since none of our patients were hypoglycemic during the testing or previous evenings. Serum cortisol levels at dawn rose earlier and growth hormone concentrations were higher in the diabetic patients than in the control subjects. Thus, both of these hormones may have contributed to the dawn phenomenon. The design of the present study does not allow, however, for definite conclusions regarding the role of these individual hormones, and their contribution in the previous literature remains controversial.[3,21–25]

Plasma glucose levels remained unchanged until 4 a.m., indicating an adequate insulin delivery until that time. Thereafter, simultaneous with the rise in serum cortisol levels, blood glucose began to rise when the insulin delivery rate was kept constant. The rises in glucose production and plasma glucose were prevented by accelerating insulin delivery. Thus, the dawn phenomenon was due to a failure to step-up the insulin infusion rate toward the morning hours. One can speculate that, at least in some patients, increased amounts of insulin are needed (particularly in the portal circulation) to prevent the stimulatory effect of counterregulatory hormones on hepatic glucose production in the early morning.

In spite of a 50% rise in insulin delivery rate, plasma free insulin levels remained unchanged and similar to or slightly lower than during the constant rate infusion. These data confirm previous observations that free insulin levels fail to increase at dawn despite higher subcutaneous or intravenous insulin infusion rates.[17,20,22,25] Several factors may contribute to this. First, when the basal infusion rate into subcutaneous tissue is increased, it takes 4–7 h to build up a new depot and reach a new steady-state condition.[26,27] Second, a number of studies have demonstrated augmented clearance of insulin during the early morning.[17,20,22] Most of the clearance occurs in the liver, which takes up 40–60% of peripherally infused insulin. Moreover, the amount of insulin removed by the liver rises in proportion to the increment of the infusion rate.[28] In keeping with this, a decline in hepatic glucose production indicates enhanced insulin action at the site of the liver during accelerated insulin infusion. Thus, increased storage in the subcutaneous depot and enhanced removal by the liver could explain, at least in part, the failure to detect a rise in peripheral free insulin levels. Finally, the current methodology for free insulin determination may not be sensitive enough to reveal small changes in ambient free insulin levels.

Taken together, the early morning rise in blood glucose in diabetic patients treated with continuous insulin infusion is associated with enhanced glucose production, rather than subnormal utilization. When the insulin delivery rate is increased, the dawn phenomenon can be abolished. However, since the dawn phenomenon does not occur in all patients and its reproducibility is still poorly understood, nocturnal hyperglycemia has to be monitored carefully in order to detect patients with the dawn phenomenon, and to preprogram their insulin infusion rate appropriately.

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