Morning Hyperglycemic Excursions

A constant failure in the metabolic control of non–insulin-using patients with type 2 diabetes

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OBJECTIVE — To determine whether, over daytime, one or several hyperglycemic excursions exist that can be general failures in the glycemic control of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — In 200 non–insulin-using patients with type 2 diabetes, diurnal plasma glucose and insulin profiles were studied. Plasma glucose concentrations were measured after an overnight fast (at 8:00 A.M. immediately before breakfast), during the postprandial period (at 11:00 A.M. and 2:00 P.M.), and during the postabsorptive period (at 5:00 P.M., extended postlunch time).

RESULTS — In the population considered as a whole, prelunch glucose concentrations (12.0 mmol/l) were found to be significantly increased ($P < 0.0001$) when compared with those observed at 8:00 A.M. (8.8 mmol/l), at 2:00 P.M. (10.5 mmol/l), and at 5:00 P.M. (8.6 mmol/l). Similar significant excursions ($P < 0.0001$) in prelunch glucose were observed within subsets of patients selected from the following criteria: *1*) body weight, *2*) HbA_{1c}, *3*) categories of treatment, and *4*) residual β-cell function. From the calculation of areas under the daytime glucose curves, the relative contributions of postprandial and fasting glucose to the total glucose increment were found to be similar.

CONCLUSIONS — High plasma glucose excursions over morning periods seem to be a permanent failure in non–insulin-using patients with type 2 diabetes, whatever the clinical (BMI), biological (HbA_{1c}), therapeutic, and pathophysiological (residual β-cell function) status. Midmorning glucose testing should be recommended for detecting such abnormalities and for correcting them with appropriate therapies.

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The influence of postprandial glycemic excursions on the overall glycemic control of type 2 diabetic patients remains a subject of controversy, even though the data from studies of 24-h plasma glycemic patterns in patients with mild type 2 diabetes seem to indicate that postprandial hyperglycemia contributes approximately 30–40% of the total daytime hyperglycemia (1,2). Such observations are in agreement with the fact that, in normally fed individuals who eat three meals per day at relatively fixed hours, the total duration of postprandial periods (from 3 to 4 h each) covers a third to a full half-day period of time (3). A few years ago, by analyzing the diurnal blood glucose profiles in type 2 diabetic patients, we observed that in all diabetic individuals, blood glucose concentrations increased during the morning period and remained elevated over a time interval from breakfast to lunch, whereas progressive improvements in blood glucose were observed in more than two-thirds of the patients during the second part of the diurnal period (4). Such observations suggest that abnormally high and sustained postbreakfast hyperglycemia can exert a deleterious effect on the overall glycemic control of type 2 diabetic patients, thus explaining that some patients with apparently fair control, according to results of blood glucose at fasting, are found to be inadequately controlled when tested for glycated hemoglobin (5). To gain further insight into the questions raised first by the relative contributions of fasting and postprandial hyperglycemia and second by the assessment and control of plasma glucose excursions at selected time points of the day in non–insulin-using patients with type 2 diabetes (6), we were led to study the diurnal blood glucose profiles in a large population of type 2 diabetic patients investigated at different levels of diabetic control and body weight, at various degrees of residual β-cell function, and submitted to different types of treatments with either diet alone or different combinations of oral blood glucose–lowering drugs.

RESEARCH DESIGN AND METHODS

Patients

Participants in the study were 200 type 2 diabetic patients (95 men, 105 women) who were entered consecutively after recruitment from the out patient clinic of the Metabolic Disease Department of the University Hospital of Montpellier (Montpellier, France). Eligibility for the study was based on a diagnosis of diabetes for at least 6 months using the new criteria (7). The subjects could be treated by diet alone or with a stable dose of metformin (two times per day at a total daily dose of 1,700 mg), glyburide (two or three times per day at a total daily dose ranging from 5 to 15 mg), or both, provided that the weight-controlling diet and/or the drug regimen had been kept constant for at least 3 months before the study. Patients

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who were being treated with acarbose or insulin were excluded. Furthermore, all patients who exhibited a variation in HbA_{1c} >0.5% within 3 months before the study were not included in the analysis. None of the patients suffered from clinical symptoms of gastroparesis. The study was conducted in accordance with the 1964 Declaration of Helsinski and the French Guidelines for Good Clinical Practice in type 2 diabetes (8), after the patients had given their informed consent.

The 200 patients included in the study were further divided into several subsets selected from the following criteria: *1*) body weight according to whether patients were obese (BMI ≥30 kg/m^2, group A, n = 97) or not (BMI <30 kg/m^2, group B, = 103); *2*) HbA_{1c} levels according to whether patients exhibited good (HbA_{1c} <7%, group I, n = 36), fair (7% ≤ HbA_{1c} ≤ 8%, group II, n = 29), or poor metabolic control (HbA_{1c} >8%, group III, n =135; most patients of this group, 99 of 135, were treated with maximal daily doses of metformin 1,700 mg and glyburide 15 mg and were waiting for complementary treatments such as insulin addition to or substitution for failing oral antidiabetic drugs); *3*) categories of antidiabetic treatments according to whether patients were treated with diet alone (group 1, n = 36), with a monotherapy (either metformin or glyburide, group 2, n = 42), or with a combination of metformin and glyburide (group 3, n = 122). In addition, the patients were separated into two groups according to whether they retained a sufficiently high residual insulin secretion rate to respond adequately to diets and/or oral medications. According to the data of the U.K. Prospective Diabetes Study (UKPDS) (9,10), we defined the first (group a, n = 124) and second groups (group b, n = 76) according to β-cell function ≥40% or <40%, respectively. The calculation of the β-cell function was based on the Homeostasis Model Analysis Assessment (HOMA), as described initially by Matthews et al. (11) and further confirmed by others (12,13). The value of the β-cell function (%) was given by the following formula: 20 × plasma insulin concentration/(plasma glucose – 3.5). Plasma insulin and glucose concentrations were measured at fasting and were expressed as μU/ml and mmol/l, respectively.

Protocol of the study and analytical procedures

On the test day, all patients were admitted to the outpatient clinic at 7:30 A.M. after an overnight fast and were hospitalized for the entire period of the study, i.e., up to the last blood sampling at 5:00 P.M. Blood samples were drawn at 3-h intervals from 8:00 A.M. to 5:00 P.M. The first sample was collected before breakfast at 8:00 A.M., the second was collected before lunch at 11:00 A.M., and the third was collected 2 h after the beginning of lunch, i.e., at 2:00 P.M. The last sample was collected at 5:00 P.M. All blood samples were further analyzed for plasma glucose determinations using the standard glucose oxidase method and for plasma insulin concentrations using a radioimmunoassay with cross-reactivity with proinsulin (DiaSorin, Vercelli, Italy). Intra-assay and interassay coefficients of variation were 6.6 and 6.2%, respectively, at mean concentration of 24 μU/ml. HbA_{1c} measurement was determined from the first blood sample using a high-pressure liquid chromatography assay (normal range 4–6%). Patients were asked to eat a test breakfast at 8:00 A.M., immediately after the first blood sampling, and a test lunch at 12:00 A.M. All meals were prepared at the University Hospital of Montpellier. The test breakfast consisted of semi-skimmed milk (300 ml), white bread (50 g), and butter (10 g), and the test lunch included meat (125 g), vegetables (200 g), boiled potatoes (100 g), vegetable oil (10 g), cheese (30 g), one apple (raw, peeled, 150 g), and white bread (25 g). The content of each meal was estimated from a nutrient database obtained from French composition tables (CIQUAL) (14) and Southgate's tables (15). The energy intake for breakfast was 350 kcal (1,460 kJ), with 44 g (50% of calories) carbohydrates (mean meal glycemic index = 90), 13 g fats, 14 g proteins, and 2 g dietary fibers. The energy intake for lunch was 670 kcal (2,800 kJ), with 67 g (40% of calories) carbohydrates (mean meal glycemic index = 80), 24 g fats, 47 g proteins, and 9 g dietary fibers. Glycemic index for mixed meals were calculated by using the method described by Wolever (16). All breakfasts and lunches were eaten within a period of <30 min. On the study day, patients were maintained on their usual treatment with oral antidiabetic drugs, and moderate physical activity such as walking was allowed between blood samplings. Taking into account that each postprandial state with respect to glucose covers a 3- to 4-h period after the beginning of meal ingestion and is followed by a postabsorptive period lasting 6 h (3), the four glycemic values of the so-called diurnal blood glucose profiles can be defined as follows: *1*) the prebreakfast value at 8:00 A.M. reflects the "real" fasting state; *2*) the extended postlunch value at 5:00 P.M. corresponds to a postabsorptive period; and *3*) the prelunch (at 11:00 A.M.) and postlunch (at 2:00 P.M.) values are a reflection of postprandial periods after breakfast and lunch, respectively.

The diurnal blood response to meals was estimated as a whole by calculating the incremental area under the daytime blood glucose curve from 8:00 A.M. to 5:00 P.M. Two areas were calculated geometrically, ignoring the area below the baseline value. The first area (S1) was calculated above a baseline level equal to the fasting plasma value and was therefore considered a reflection of the postprandial glycemic responses to breakfast and lunch. The second area (S2) was calculated above a baseline level equal to 6.1 mmol/l (110 mg/dl), reflecting both the increases in fasting and postprandial plasma glucose. Therefore, the difference S2 – S1 can be considered an assessment of the increment in fasting plasma glucose values. As a result, the relative contributions of postprandial and fasting plasma glucose to the total plasma glucose increment were calculated using the following equations: S1/S2 × 100 for the postprandial contribution and S2 – S1/S2 × 100 for the fasting contribution.

Statistical analysis

All results are given as means ± SEM. Sets of data at the different time points of the day (i.e., glycemia and insulinemia at 8:00 A.M., 11:00 A.M., 2:00 P.M., and 5:00 P.M.) were subjected to repeated-measures ANOVA with time as the within-subject factor and BMI, treatment, β-cell function, or diabetic control as the between-subject factor. All pairwise comparisons of individual means for effects found to be significant in the ANOVA were performed using a Bonferroni correction factor. For insulinemia, a comparison at each time point was also performed using Bonferroni test. In the different groups, χ^2 test was used for comparing the proportions of patients with plasma glucose concentrations higher at prelunch than at postlunch

Table 1—*Clinical and laboratory data*

	Group identification										
		Body weight (BMI, kg/m^2)		HbA_{1c} (%)			Categories of treatment			Residual β-cell function (%)	
Patient characteristics	Entire population	≥30 A	<30 B	<7 I	7–8 II	>8 III	Diet alone 1	Monotherapy 2	Combined therapy 3	≥40 a	<40 b
Number of patients tested	200	97	103	36	29	135	36	42	122	124	76
Age (years)											
Mean	59.7	58.1	61.2	53.9	61.8	60.8	54.0	58.3	61.9	58.5	61.8
SEM	0.7	1.1	1.0	1.9	1.5	0.9	2.1	1.7	0.8	1.0	1.0
BMI (kg/m^2)											
Mean	30.8	35.6	26.4	31.3	32.2	30.4	31.9	31.3	30.4	32.1	28.8
SEM	0.4	0.6	0.2	1.3	1.2	0.5	1.4	1.0	0.5	0.6	0.5
HbA_{1c} (%)											
Mean	8.56	8.57	8.55	6.12	7.34	9.47	7.0	8.28	9.12	8.15	9.24
SEM	0.12	0.18	0.17	0.09	0.06	0.10	0.25	0.24	0.14	0.15	0.19
β-cell function (%)											
Mean	71.9	81.4	63.0	110.3	79.5	60.0	99.9	94.4	55.9	100.6	25.0
SEM	5.3	6.9	7.8	12.9	11.5	6.2	12.2	13.6	5.9	7.3	0.9
Insulin resistance											
Mean	5.0	5.6	4.4	3.5	4.7	5.5	4.3	5.3	5.1	5.2	4.6
SEM	0.2	0.4	0.3	0.3	0.5	0.3	0.5	0.5	0.3	0.3	0.3

times. The relative contributions of postprandial and fasting plasma glucose to the total glucose increments were compared using the Student's *t* test for paired data. Analyses were performed with Statview statistical software, version 5 for Macintosh (SAS Institute, Cary, NC).

RESULTS

Main clinical and laboratory data are reported in Table 1.

Comparison of plasma glucose and insulin concentrations at the different time points of the day

The diurnal profiles for plasma glucose and insulin concentrations (Fig. 1) differed significantly with time ($P < 0.0001$), with significant effects of BMI ($P = 0.036$ for glucose, $P = 0.010$ for insulin) and treatment ($P < 0.0001$ for glucose, $P = 0.0036$ for insulin). Plasma glucose concentrations differed significantly with diabetic control ($P < 0.0001$) and β-cell function ($P < 0.0001$), whereas plasma insulin did not. In the population considered as a whole, prelunch plasma glucose concentrations at 11:00 A.M. were significantly increased ($P < 0.0001$) compared with those observed at the other time points (8:00 A.M., 2:00 P.M., and 5:00 P.M.). Similar statistical significances were observed within the different subsets of patients: all mean plasma glucose concentrations at prelunch time were significantly higher than those observed at the other time points. To determine whether the peak values as observed at prelunch time were dependent on parameters such as BMI, HbA_{1c}, residual β-cell function, and categories of antidiabetic treatment, we calculated the proportions of patients with plasma glucose concentrations at prelunch time above that observed at postlunch time. No statistical differences were found between percentages, whatever the group of patients considered: $\chi^2 = 1.92$ ($P = 0.19$) for BMI; $\chi^2 = 0.11$ ($P = 0.87$) for residual β-cell function; $\chi^2 = 0.01$ ($P = 0.99$) for HbA_{1c}; and $\chi^2 = 3.98$ ($P = 0.14$) for categories of treatment.

In both the entire population and the different groups (BMI and treatment), plasma insulin concentrations reached peak values during the second part of the diurnal period, being higher at 2:00 P.M. and 5:00 P.M. than at 8:00 A.M. and 11:00 A.M. Prelunch and postlunch plasma insulin concentrations differed significantly with treatment; the lowest values were observed in patients submitted to a combined therapy. BMI significantly affected fasting, prelunch, and extended postlunch plasma insulin concentrations; the higher values were observed in patients with BMI ≥30 kg/m^2. No influence was observed with HbA_{1c}.

Respective contributions of fasting and postprandial glucose increment to the overall diabetic control over the diurnal period

The areas under curve (AUC) above fasting glucose (S1) and >6.1 mmol/l (S2) were 18.6 ± 1.1 and 40.0 ± 1.8, mmol · h^{-1} · l^{-1}, respectively; the difference S2 – S1 was equal to 21.5 ± 1.5 mmol · h^{-1} · l^{-1}. The respective contributions of S1 (postprandial glucose increment) and S2 – S1 (fasting glucose increment) to the total glucose increment (S2) were equal to 53.5 ± 2.2 and 46.5 ± 2.2%. No statistical differences were observed first between the absolute values S1 and S2 – S1 and second between the relative contributions of S1 and S2 – S1 to S2.

CONCLUSIONS

— The present results indicate clearly that prelunch plasma glucose concentrations are higher than fasting, postlunch, and extended postlunch plasma glucose values in type 2 diabetic patients who have never been treated with either insulin or α-glucosidase inhibitors. The results are independent of the pa-

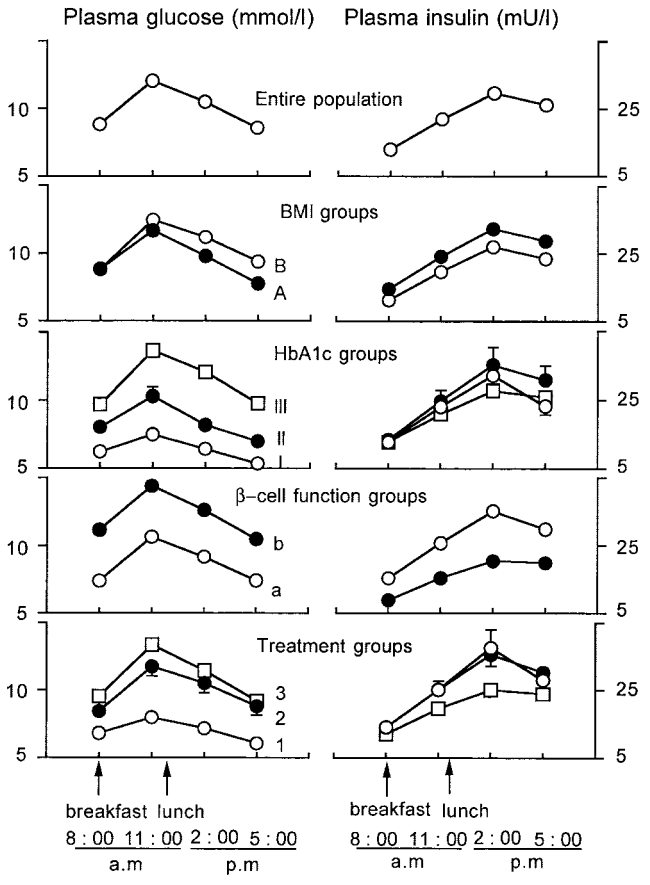

Figure 1—*Diurnal profiles of plasma glucose and insulin concentrations in the entire population; BMI subsets A (≥30 kg/m^2) and B (<30 kg/m^2); HbA_{1c} subsets I (<7%), II (7–8%), and III (>8%); residual β-cell function subsets a (≥40%) and b (<40%); and treatment subsets 1 (diet alone), 2 (monotherapy), and 3 (combined therapy).*

tients' characteristics: *1*) clinical status as estimated from BMI; *2*) diabetic control as estimated from HbA_{1c} levels; *3*) residual β-cell function as quantified from Homeostasis Model Analysis Assessment (HOMA); and *4*) categories of treatment such as diet alone and/or oral antidiabetic drugs given as either monotherapy or combined therapy. The abnormally high postbreakfast hyperglycemic excursions and the differences between midmorning and postlunch plasma glucose values can be attributed to several mechanisms, because glucose responses to meals result from an interplay between insulin sensitivity (peripheral tissue and liver) and insulin secretory dysfunction (17). The results of a recent study seem to indicate that the insulin sensitivity of hepatic glucose production plays the most important role in the regulation of blood glucose response during oral glucose tolerance test in patients suffering from either impaired glucose tolerance or mild diabetes (18). Furthermore, it has been demonstrated that the hepatic glucose output of type 2 diabetic patients is subject to circadian variations (19) characterized by a peak value at the end of the overnight fast and a progressive decline over daytime to reach a nadir in the late afternoon (19). Such abnormalities certainly contribute to the poor diabetic control observed during the morning period from breakfast to lunch. The better postprandial glucose values observed after lunch could be due to improvements in both hepatic glucose production and insulin sensitivity in the afternoon. Even though other explanations remain possible, our results indicate that carbohydrate intake at breakfast (44 g in the present study) is of little relevance compared with the other potential pathophysiological mechanisms, because glucose levels are higher in the morning despite lower carbohydrate intake than at lunch (67 g).

Other comments arise from our data. One of the main findings is that the shapes of diurnal glucose profiles are similar for all the individualized subgroups. This observation is particularly true for both groups II (HbA_{1c} 7–8%) and III (HbA_{1c} >8%). Despite a possible Staub-Traugott effect (20,21) (glucose concentrations were found lower after lunch than after breakfast), such findings suggest that high plasma glucose concentrations during the morning period at 11:00 A.M. probably have a remnant deleterious influence on the glycemic control over the subsequent period of daytime, at least up to 5:00 P.M. However, even though the unsatisfactory control of midmorning plasma glucose concentrations is one of the permanent failures in metabolic control, especially in groups II (10.3 ± 0.7 mmol/l) and III (13.7 ± 0.3 mmol/l), it must be mentioned that both groups also exhibited high fasting plasma glucose values: 8.0 ± 0.4 mmol/l for group II and 9.7 ± 0.3 mmol/l for group III. Therefore, it is suggested that all therapeutic strategies recommended for controlling midmorning blood glucose excursions (i.e., α-glucosidase inhibitors, new short-acting secretagogues, or injections of short-acting insulin analogs) should also be combined with appropriate treatments (22–24) for reducing fasting plasma glucose levels to near-normal values. Such recommendations seem to be supported by the fact that the respective contributions of fasting and postprandial plasma glucose increments to the total plasma glucose increment during the diurnal period are approximately similar.

In conclusion, our results indicate that unsatisfactory control of midmorning plasma glucose concentrations is a permanent failure in metabolic control of non–insulin-using type 2 diabetic patients. Therefore, it is suggested that self-monitoring or laboratory determinations of midmorning plasma glucose should be recommended at regular time intervals, particularly in patients who are not adequately controlled in terms of HbA_{1c} (25). Such midmorning determinations, combined with those of fasting glucose, can be helpful for adjusting treatment of type 2 diabetic patients.

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