The Loss of Postprandial Glycemic Control Precedes Stepwise Deterioration of Fasting With Worsening Diabetes

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OBJECTIVE — The aim of the study was to determine whether the loss of fasting and postprandial glycemic control occurs in parallel or sequentially in the evolution of type 2 diabetes.

RESEARCH DESIGN AND METHODS — In 130 type 2 diabetic patients, 24-h glucose profiles were obtained using a continuous glucose monitoring system. The individuals with type 2 diabetes were divided into five groups according to A1C levels: 1 (<6.5%, $n = 30$), 2 (6.5–6.9%, $n = 17$), 3 (7–7.9%, $n = 32$), 4 (8–8.9%, $n = 25$), and 5 (≥9%, $n = 26$). The glucose profiles between the groups were compared. The overall glucose concentrations for the diurnal, nocturnal, and morning periods, which represent the postprandial, fasting, and the dawn phenomenon states, respectively, were also compared.

RESULTS — Glucose concentrations increased steadily from group 1 to 5 in a stepwise manner. The initial differences in mean glucose concentrations reaching statistical significance occurred *1*) between groups 1 and 2 (6.4 vs. 7.7 mmol/l, $P = 0.0004$) for daytime postprandial periods, followed by differences; *2*) between groups 2 and 3 (7.5 vs. 9.3 mmol/l, $P = 0.0003$) for the morning periods (dawn phenomenon); and finally *3*) between groups 3 and 4 (6.3 vs. 8.4 mmol/l, $P < 0.0001$) for nocturnal fasting periods.

CONCLUSIONS — The deterioration of glucose homeostasis in individuals with type 2 diabetes progressed from postprandial to fasting hyperglycemia following a three-step process. The first step related to the three diurnal postmeal periods considered as a whole, the second step occurred during the morning period, and the third and final step corresponded to sustained hyperglycemia over the nocturnal fasting periods. Such a description of the key stages in the evolution of type 2 diabetes may be of interest for implementing antidiabetes treatment.

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The steady decline in the quality of glucose homeostasis (1) as observed in type 2 diabetes results from an increasing defect (2) in both insulin sensitivity and secretion (3). The data from the UK Prospective Diabetes Study indicate that the gradual increase in both A1C levels and fasting glucose concentrations is mainly due to a relentless linear deterioration in β-cell function from the time of diagnosis. In contrast, the years that precede the development of type 2 diabetes are characterized by a progressive decline in both insulin action and defects in the early phase of the insulin secretion (4,5). Such abnormalities lead to a progressive transition from normal glucose tolerance to impaired glucose tolerance and finally to frank type 2 diabetes. As impaired glucose tolerance is acknowledged as a prediabetic stage, it has been postulated that losses of postprandial glucose control occur before deterioration in fasting glucose concentration (4,6,7). In a previous study (8), we have demonstrated that postprandial glucose increments are predominant contributors to the overall hyperglycemia in patients with an A1C <7.3%, while fasting increments represent the major contributor to worsening diabetic control. These results, along with the findings of others (9), indicate that postprandial glucose deteriorates before fasting glucose. However, the exact sequence of events in the deterioration of glycemic status is not completely understood. It remains unclear whether the loss in glucose control during fasting or postprandial periods occurs in parallel or sequentially. Furthermore, it is known that postmeal glucose excursions after breakfast, lunch, and dinner are not equally affected and may deteriorate at different rates over the time course of the disease, which may also differ across different population groups. To gain further insight into these questions, which are of practical importance for tailoring the introduction of available antidiabetes treatments, we used the CGMS data (10) in 130 patients with type 2 diabetes. The glucose profiles obtained during this investigation were further analyzed after the patients had been stratified into 5 groups according to A1C levels.

RESEARCH DESIGN AND METHODS

— A total of 130 individuals with type 2 diabetes (100 men and 30 women) were entered consecutively into the study with an A1C ranging from 5.2 to 12.5%. Diabetes duration from diagnosis ranged from newly diagnosed to 36 years (means ± SE duration, 7.0 ± 0.8 years). None were on insulin therapy, with treatment consisting of diet alone or diet plus different individual or combinations of oral antidiabetes drugs (Table 1). Exclusion criteria included patients who had experienced an acute intercurrent illness or who had been treated with steroids during the preceeding 3-month period. Also, all individuals treated with α-glucosidase inhibitors or glinides were excluded to avoid any bias in the interpretation of postprandial glucose excursions. The study was conducted only after the patients had given their oral informed consent in accordance with the

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Abbreviations: CGMS, continuous glucose monitoring system; FPG, fasting plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Clinical and laboratory data*

Groups	1	2	3	4	5	Entire group
A1C (%)	<6.5	6.5–6.9	7–7.9	8–8.9	≥9	
Patients tested (*n*)	30	17	32	25	26	130
Age (years)	58.7 ± 1.9	57.9 ± 1.7	59.6 ± 1.8	59.3 ± 2.2	61.4 ± 1.8	59.9 ± 0.8
M/F ratio	28/2	15/2	25/7	18/7	14/12	100/30
BMI (kg/m^2)	31.0 ± 1.1	29.8 ± 1.5	28.6 ± 0.7	26.3 ± 0.9	32.1 ± 1.0	29.6 ± 0.5
Systolic blood pressure (mmHg)	135 ± 3	141 ± 5	137 ± 3	133 ± 4	138 ± 3	137 ± 2
Diastolic blood pressure (mmHg)	83 ± 2	82 ± 3	79 ± 2	77 ± 2	78 ± 3	80 ± 1
Diabetes duration (years)	0.7 ± 0.3	4.4 ± 2.3	8.4 ± 1.4	10.0 ± 2.2	11.5 ± 1.7	7.0 ± 0.8
Dietary intakes						
Energy (kcal/day)	2,252 ± 94	2,299 ± 111	2,018 ± 71	2,041 ± 66	1,795 ± 80	2,069 ± 40
Carbohydrates (g/day)	263 ± 13	273 ± 15	235 ± 10	242 ± 8	205 ± 10	242 ± 5
Fats (g/day)	88 ± 4	89 ± 4	78 ± 3	79 ± 3	69 ± 3	80 ± 2
Proteins (g/day)	103 ± 3	101 ± 5	93 ± 3	90 ± 4	84 ± 3	94 ± 2
Glycemic index values						
Breakfast	79 ± 0	78 ± 0	79 ± 0	79 ± 0	80 ± 1	79 ± 0
Lunch	73 ± 0	72 ± 1	74 ± 1	73 ± 1	75 ± 1	74 ± 0
Dinner	70 ± 0	71 ± 1	71 ± 1	71 ± 1	73 ± 1	71 ± 0
Timing of meals						
Breakfast	7:48 ± 0:12	8:19 ± 0:26	8:00 ± 0:09	8:08 ± 0:11	8:17 ± 0:13	8:05 ± 0:06
Lunch	13:11 ± 0:15	13:22 ± 0:16	12:37 ± 0:07	12:58 ± 0:09	12:48 ± 0:09	12:58 ± 0:05
Dinner	19:05 ± 0:15	19:25 ± 0:16	19:30 ± 0:10	20:08 ± 0:12	19:32 ± 0:09	19:31 ± 0:06
Diabetes treatment						
Diet alone	29	11	6	4	2	52
Sulfonylurea alone	0	1	2	0	1	4
Metformin alone	0	0	4	4	1	9
Combination (sulfonylurea and metformin)	1	5	20	17	22	65
Other treatments						
Lipid-lowering drugs	18	7	13	9	14	61
Antihypertensive drugs	14	7	9	8	7	45
A1C (%)	5.9 ± 0.1	6.8 ± 0.0	7.4 ± 0.1	8.4 ± 0.1	10.1 ± 0.2	7.7 ± 0.1

Data are means ± SE or *n*.

European directives that require no approval from an ethics committee for the study design as described herein. The inclusion criteria required that the dietary and/or the drug regimens had been kept constant for at least 3 months before the study.

Protocol of the study

The subcutaneous interstitial glucose was monitored on an ambulatory basis over a period of 3 consecutive days by using the second-generation Minimed CGMS (CGMS; Northridge, CA) (10). The implantation of the sensor occurred at the outpatient clinics of either the Department of Metabolism (Montpellier, France) for 72 patients or the Diabetes Research Unit (Cardiff, U.K.) for 58 patients. The sensor was inserted on day 0 and removed on day 3 at midmorning times. The data were downloaded on a computer for evaluation of the glucose profiles to include estimation of glucose variations limited to data collected on days 1 and 2. The patients were instructed to maintain their usual diet and treatment and to not modify their meal timing over the 3-day period of continuous monitoring. The newly diagnosed diabetic patients were maintained on their usual diet. In the other patients, isocaloric and moderately hypocaloric diets were prescribed at for least 3 months before the investigation, according to whether the BMI was <25 or ≥25 kg/m^2. The caloric intakes estimated from Schofield's formula (11) were multiplied by a coefficient of 1.55, corresponding to the sedentary physical activity as observed in most of our patients (12). The proportions of calories provided from carbohydrates was set at 45 and 50% in patients with BMI <25 and ≥25 kg/m^2, respectively. The calories contributed by fats was ~35% regardless of the patient's weight, with proteins providing 20 and 15% in those with a BMI <25 or ≥25 kg/m^2, respectively. The content of food was determined by a dietitian at the end of the 3-day study periods. All patients who differed by >10% from the theoretical energy and carbohydrate intakes were excluded from the study. The glycemic index values for the different meals were calculated using the method described by Wolever (13). The mean energy, the nutrient content, the mean glycemic index values, and the mean timings of meals are indicated in Table 1. The characteristic glucose pattern of each individual was calculated by averaging the profiles obtained on study days 1 and 2. On day 0, after an overnight fast, venous blood samples were drawn into tubes containing EDTA for A1C determination.

Laboratory measurements

A1C measurements were made by using either a high-performance liquid chromatography assay (Menarini Diagnostics, Florence, Italy in Montpellier) (14) or

TOSOH HLC-723 G7 analyzer in Cardiff, U.K. (15). For both methods, the intra- and interassay coefficient of variations (CVs) were <2% with a nondiabetic reference range of 3.7–5.1% A1C. Both assay methods were certified as being in conformity with the Diabetes Control and Complications Trial standards (16), which recommend CVs <5% and ideally <3%. The two assays were compared in 44 patients and found to be highly correlated ($R^2 = 0.98$); the relationship was described by an identity line: $Y = -0.133 + 1.049\ X$, with Y and X corresponding to the Menarini and TOSOH assays, respectively.

Analysis of the CGMS data

The subjects were divided into five groups defined according to the A1C concentration: group 1, A1C <6.5% ($n = 30$); group 2, A1C 6.5–6.9% ($n = 17$); group 3, A1C 7–7.9% ($n = 32$); group 4, A1C 8–8.9% ($n = 25$); and group 5, A1C ≥9% ($n = 26$). The rationale for selection of the different groups was based on the fact that A1C goals for patients have been set at <6.5% by the International Diabetes Federation (17) and at 7% by the American Diabetes Association (18), respectively, and up until 2002, 8% was the A1C threshold value selected by the American Diabetes Association for additional therapeutic intervention (19). In the patients of groups 1 and 2, a subanalysis of the CGMS data was done after excluding those patients who were on pharmacological treatment to evaluate the changes in glycemic profiles in patients treated with diet alone (i.e., 29 and 11 patients in subgroups 1 and 2, respectively).

Mean glucose concentrations in each group were calculated by taking two time points as reference. Midnight (i.e., 0000 h) was taken as the start of the nocturnal fasting period while immediate prebreakfast times were considered as time 0 of the daytime postprandial period. Because the study was conducted in real-life conditions, meal times differed between both study days and patients. Therefore, glucose sensor values of each participant were read for each recording on days 1 and 2 at prebreakfast times, after satisfactory concordance ($r > 0.8$) had been validated between the glucose values calculated by the sensor and those obtained from capillary blood measurements. The mean of the two values as obtained were further averaged in the 130 patients to determine the mean prebreakfast time point that was set at 0805 h following this calculation. Considering that the postprandial state was defined as a 3- to 4-h period following ingestion of a meal (20) and after having calculated that the average timings of the two other meals, i.e., lunch and dinner, were found at 1258 h and 1931 h, respectively, in the population considered as a whole, we have estimated that the period of daytime starting with breakfast (i.e., prebreakfast time) and ending 3–4 h after dinner covered the entire postprandial period of the day, while the remaining period beginning at midnight and ending at prebreakfast time corresponds to the nocturnal fasting period. In addition to the daytime postprandial and nocturnal fasting periods, we defined a morning period starting 1 h before breakfast and ending 3 h later, corresponding to the "dawn" or "extended dawn" phenomenon, which appears to play a crucial role in determining the diabetic control of many patients with type 2 diabetes (21,22). The glucose values obtained from the CGMS data were averaged for the three periods as described above.

Statistical analysis

Results are given as means ± SE or as geometric mean and 95% CI according to whether the variables were normally distributed. Log-transformed glucose concentrations over the three study periods were tested for normal distribution by using the test statistic for the Kolmogorov-Smirnov goodness-of-fit test for continuous data (23). Comparisons between mean glucose values in the different groups of patients were made using one-way ANOVA followed by Bonferroni-Dunn post hoc testing. Statistical comparisons were considered significant when P values were $\leq 0.05/n$ (n = number of comparisons). Analyses were performed with the STATVIEW statistical package, version 5 for Macintosh (SAS Institute, Cary, NC).

RESULTS

— The main clinical and laboratory data are included in Table 1. The known duration of diabetes (years from diagnosis) progressively increased from group 1 to group 5. The average values of the 24-h glucose profiles in the five groups of individuals with type 2 diabetes are represented in Fig. 1. The results show a progressive deterioration of the glycemic profiles from group 1 to 5 associated with increasing levels of A1C. This progressive deterioration from group 1 to 5 was statistically and quantitatively analyzed step by step (Fig. 2). The first statistical significant change in mean glucose levels was for the daytime postprandial period (Fig. 2*A*), followed by the morning period (Fig. 2*B*), and finally the nocturnal fasting period (Fig. 2*C*). The results indicate that statistical changes occurred in a stepwise manner.

Comparison of daytime postprandial periods

As indicated in Fig. 2*A*, the mean glucose concentrations for the daytime postprandial periods increased steadily from group 1 to 5. The first significant difference was observed between group 1 (A1C <6.5%) and group 2 (A1C between 6.5 and 6.9%), i.e., 6.4 mmol/l (95% CI 6.1–6.7) vs. 7.7 mmol/l (7.0–8.4), respectively ($P = 0.0004$) (Table 2).

Comparison of morning periods (dawn phenomenon)

As shown in Fig. 2*B*, the mean glucose concentrations for the morning periods were not statistically different between groups 1 and 2. The first difference occurred only when group 2 (A1C between 6.5 and 6.9%) and group 3 (A1C between 7 and 7.9%) were compared: 7.5 mmol/l (95% CI 6.8–8.3) vs. 9.3 mmol/l (8.7–10.0) ($P = 0.0003$), even though the mean glucose concentrations for the morning period continued to increase with worsening A1C as seen in both groups 4 and 5, i.e., when A1C values were >8 and 9%, respectively (Table 2).

Comparison of nocturnal fasting periods

As indicated in Fig. 2*C*, the mean glucose concentrations for the nocturnal fasting periods remained at near-normal levels as long as A1C levels were <8%. The first difference was noted when group 3 (A1C between 7 and 7.9%) and group 4 (A1C between 8 and 8.9%) were compared (6.3 mmol/l [95% CI 5.7–6.9] vs. 8.4 mmol/l [7.7–9.3], $P < 0.0001$), even though further deterioration occurred in group 5 (Table 2).

Comparison of glycemic profiles in the patients of subgroups 1 and 2 who were treated with diet alone

Mean glucose concentrations over nocturnal periods were similar in both subgroups, while the mean glucose concentrations over postprandial periods of daytime were higher in subgroup 2 (7.9 mmol/l [95% CI 7.2–8.9], $n = 29$) than in

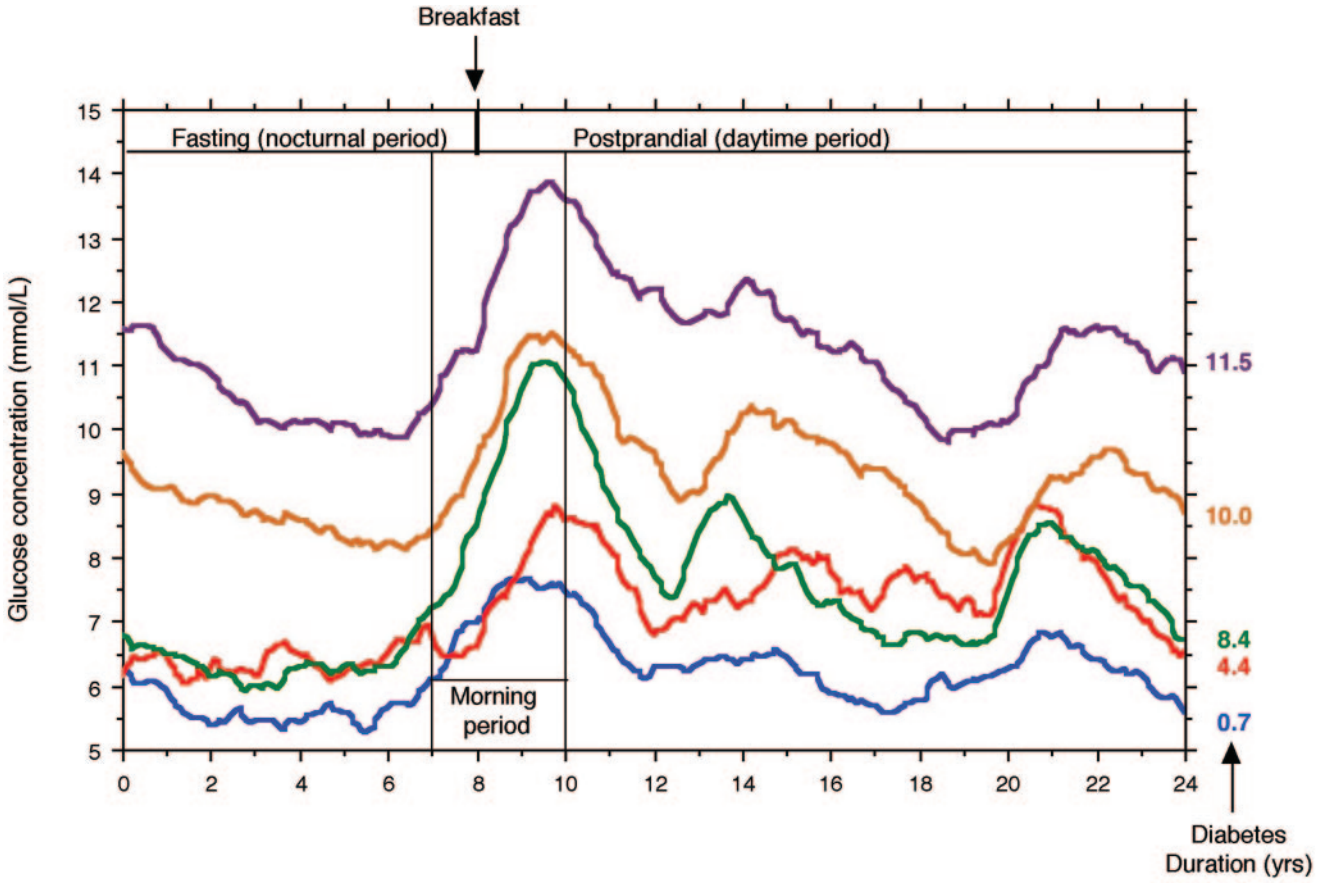

Figure 1—*Twenty-four hour recordings from the CGMS in the five groups of patients with type 2 diabetes. Curve 1 (blue): A1C <6.5%; curve 2 (red): ≤ 6.5% to <7%; curve 3 (green): ≤7% to <8%; curve 4 (orange): ≤8% to 9%; curve 5 (purple): ≥9%.*

subgroup 1 (6.3 mmol/l [6.1–6.7], n = 11, P = 0.0002).

CONCLUSIONS — The results from this study indicate that a gradual loss in daytime postmeal glycemic control precedes a stepwise deterioration in nocturnal fasting periods with worsening diabetes. The morning periods (dawn phenomenon) are interposed as an intermediary step between the nocturnal and diurnal periods. Furthermore, these results demonstrate that the nocturnal fasting glycemic control remains essentially unchanged as long as the A1C levels remained <8%. In contrast, the glycemic control during the postprandial periods was subject to early deterioration occurring as A1C levels exceeded 6.5%. Therefore, patients who had near-normal glucose values at prebreakfast time (e.g., patients in group 2) exhibited abnormal elevation of glucose levels after meals. These results seem to be in agreement with the observation that in "treat-to-target" interventional trials (24,25), similar drops in fasting glucose did not result in similar improvements in A1C. The causes of such discrepancies could probably be due to smaller reductions in postmeal glucose excursions in those patients who exhibited the smallest benefits in terms of A1C (24,25). This opinion is reinforced by the fact that, in at least two trials, it has been established that patients who achieved fasting plasma glucose (FPG) below the targets, i.e., 5.6 mmol/l (26,27), were still exhibiting A1C levels >7%. These data indicate that in those patients who fail to achieve A1C <7% but who have near-normal FPG concentrations, the failure in optimizing glycemic control is mostly due to a residual and persistent elevation in postprandial glucose following the three main meals of the day. Therefore, our own results and those of Woerle et al. (26) suggest strongly that treat-to-target treatment strategies should initially be aimed at normalizing FPG values and then reducing postprandial glucose concentrations. In the present study, patients who had an A1C <6.5% exhibited near-normal fasting glucose values and maintained their mean postprandial glucose<7.8 mmol/l. In addition, the subanalysis of the CGMS in subgroups 1 and 2 after excluding the patients who were pharmacologically treated is of particular interest since this analysis confirmed that in patients on diet alone, the first deterioration of the glycemic profile occurred during the postprandial period. As the glucose profiles of these patients were not dependent on the therapeutic choice made by their physicians for selecting the pharmacological treatment, one can consider that the observed deterioration is a reflection of the natural course of worsening diabetes. This observation is reinforced by the fact that the carbohydrate intakes were similar in these two early subgroups. While these results suggest that excessive postprandial glucose increments should be managed earlier in the course of the disease to achieve A1C <6.5%, amelioration of postprandial excursions cannot be assumed to delay the progression of the disease (28).

Another point concerns the second step in the deterioration of the glycemic profiles, i.e., the significant increase in glucose concentrations as observed during the morning periods in group 3 due to an overproduction of glucose by the liver

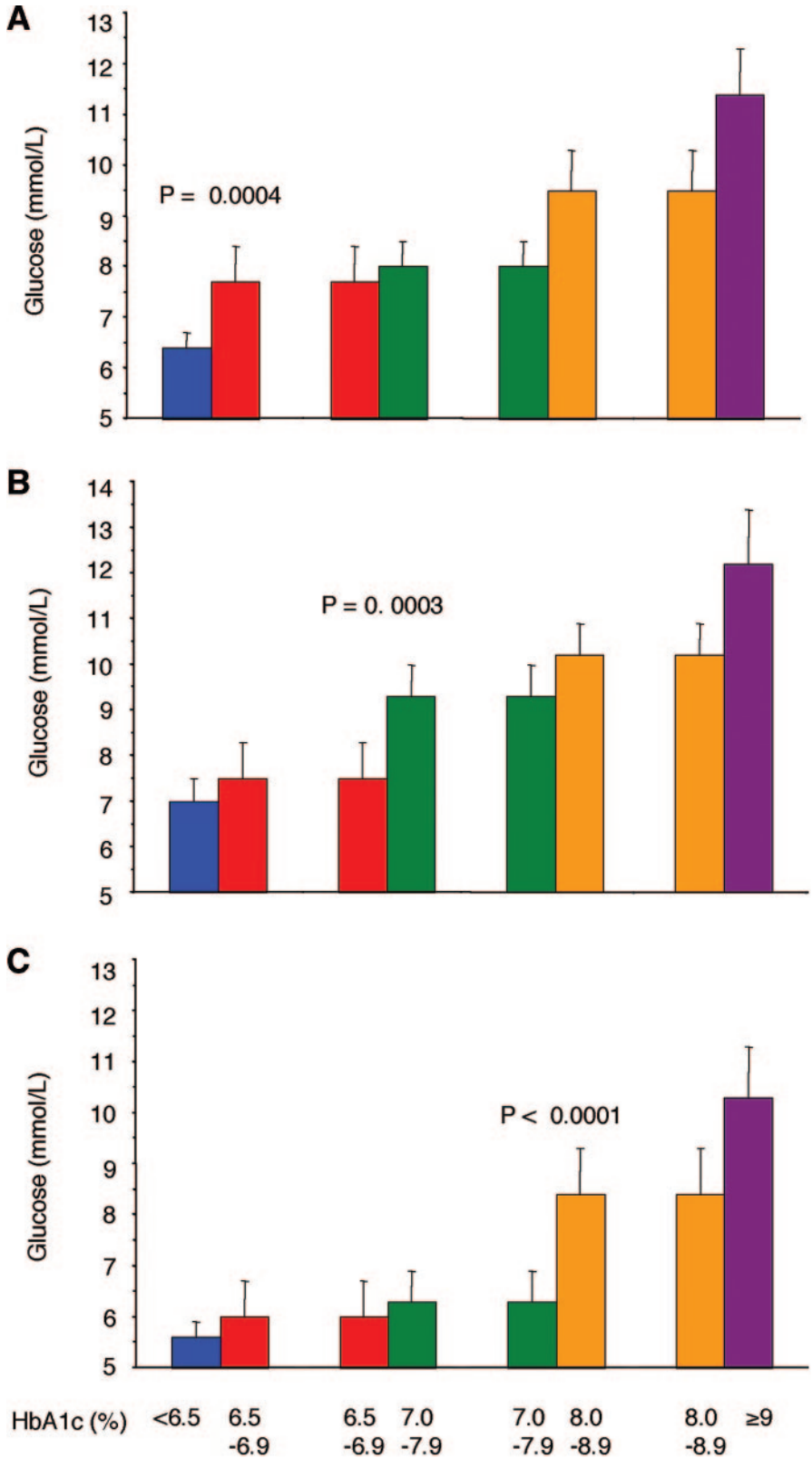

Figure 2—*Progressive deterioration of the glycemic profiles according to A1C levels in the three studied periods: daytime postmeal period* (A)*, morning period (dawn phenomenon)* (B)*, and nocturnal fasting period* (C)*. Data are geometric means of glucose concentrations and superior value of 95% CI. Only the initial differences in mean glucose concentrations reaching statistical significance are indicated. Statistical comparisons were considered significant for* $P < 0.05$/n (n = *comparison number, Bonferroni correction).*

(22). These metabolic disturbances, better known as the so-called "dawn phenomenon" (21), start at the end of the overnight fast, i.e., at prebreakfast time, but have a prolonged deleterious effect on glucose concentrations over the entire postbreakfast period. The combined effects of the dawn phenomenon and of glucose derived from the intestinal hydrolysis of breakfast carbohydrates can result in an "extended dawn phenomenon" characterized by sustained blood glucose excursions during the morning period. Our results seem to indicate that the dawn and extended dawn phenomena remained relatively controlled as long as A1C remains <7%. In contrast, in patients exhibiting A1C >7%, the metabolic abnormalities that characterize the dawn and extended dawn phenomena are no longer normalized by dietary measures and/or by treatments with oral antidiabetes drugs. In such situations, i.e., in patients with A1C between 7 and 7.9%, it remains to be seen whether treatments with once-daily injection using small doses of rapid insulin analogs or inhaled insulin at prebreakfast time should or should not be initiated to limit postbreakfast blood glucose excursions during the morning period, with the aim of achieving an A1C <6.5%, the latest target defined in the International Diabetes Federation's *Global Guideline for Type 2 Diabetes* (17). Our results might also be important for defining more precisely the time for introduction for the recently available glucagon-like peptide 1 analogs, which exert a glucose-dependent insulinotropic action (29,30). According to our results, these treatments might be particularly useful for patients with A1C levels between 7 and 8% to reduce the postbreakfast glucose excursions that are particularly marked at this stage of the disease.

Finally, in those patients in whom the A1C level was >8%, the therapeutic prerequisite is first to reduce the nocturnal hyperglycemia by using long-acting insulin analogs given before dinner or at bedtime. According to the treat-to-target concept (31), the insulin replacement therapy should target both A1C and FPG to achieve A1C ≤7% and FPG ≤5.6 mmol/l. However, even when the patients meet these objectives, it is not necessary that optimal glycemic control has been achieved. The present data indicate that one or several major glucose excursions may still occur daily in these patients and

Table 2—*Data of Fig. 2*

Groups	1	2	3	4	5
A1C (%)	<6.5	6.5–6.9	7–7.9	8–8.9	≥9
Patients tested	30	17	32	24	26
Mean glucose concentrations (mmol/l)					
Over daytime postmeal period*	6.4 (6.1–6.7)†	7.7 (7.0–8.4)	8.0 (7.6–8.5)†	9.5 (8.7–10.3)†	11.4 (10.5–12.3)
Over morning periods‡	7.0 (6.7–7.5)	7.5 (6.8–8.3)†	9.3 (8.7–10.0)†	10.2 (9.5–10.9)†	12.2 (11.1–13.4)
Over nocturnal fasting periods§	5.6 (5.3–5.9)	6.0 (5.4–6.7)	6.3 (5.7–6.9)†	8.4 (7.7–9.3)†	10.3 (9.3–11.3)

Data are geometric mean (95% CI) or *n*. *Data from breakfast to midnight. †Mean glucose concentration of the group significantly different from the following. ‡Data from 1 h before breakfast to 2 h after breakfast. §Data from midnight to breakfast.

suggest that adding prandial insulin before such meals may further improve glycemic control.

In conclusion, the monitoring of glucose patterns over 24 h indicates that the deterioration of glucose homeostasis can be approximated to a three-step process. The first step corresponds to a loss of postprandial glycemic control. The second step is characterized by a deterioration of the glycemic control during the prebreakfast and postbreakfast periods that correspond to the dawn and extended dawn phenomena (21). The final step in the deterioration of the diabetic control is represented by a sustained hyperglycemia over the nocturnal period resulting in fasting hyperglycemia. These observations should be of great interest for guiding the choice of antidiabetes therapeutic strategies during the evolution of type 2 diabetes in a attempt to achieve near normoglycemia.

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