Contributions of Fasting and Postprandial Plasma Glucose Increments to the Overall Diurnal Hyperglycemia of Type 2 Diabetic Patients

Variations with increasing levels of HbA_{1c}

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OBJECTIVE — The exact contributions of postprandial and fasting glucose increments to overall hyperglycemia remain controversial. The discrepancies between the data published previously might be caused by the interference of several factors. To test the effect of overall glycemic control itself, we analyzed the diurnal glycemic profiles of type 2 diabetic patients investigated at different levels of HbA_{1c}.

RESEARCH DESIGN AND METHODS — In 290 non–insulin- and non–acarbose-using patients with type 2 diabetes, plasma glucose (PG) concentrations were determined at fasting (8:00 A.M.) and during postprandial and postabsorptive periods (at 11:00 A.M., 2:00 P.M., and 5:00 P.M.). The areas under the curve above fasting PG concentrations (AUC_1) and >6.1 mmol/l (AUC_2) were calculated for further evaluation of the relative contributions of postprandial (AUC_1/AUC_2, %) and fasting [$(AUC_2 - AUC_1)/AUC_2$, %] PG increments to the overall diurnal hyperglycemia. The data were compared over quintiles of HbA_{1c}.

RESULTS — The relative contribution of postprandial glucose decreased progressively from the lowest (69.7%) to the highest quintile of HbA_{1c} (30.5%, $P < 0.001$), whereas the relative contribution of fasting glucose increased gradually with increasing levels of HbA_{1c}: 30.3% in the lowest vs. 69.5% in the highest quintile ($P < 0.001$).

CONCLUSIONS — The relative contribution of postprandial glucose excursions is predominant in fairly controlled patients, whereas the contribution of fasting hyperglycemia increases gradually with diabetes worsening. These results could therefore provide a unifying explanation for the discrepancies as observed in previous studies.

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The exact contribution of postprandial blood glucose excursions to the overall glycemic control of patients with type 2 diabetes remains largely undetermined (1). A few years ago in non–insulin-treated type 2 diabetic patients, we found that postlunch and extended postlunch plasma glucose (PG) concentrations were better correlated to HbA_{1c} than fasting values (2). More recently in the same type of patients, it has been reported (3) that preprandial PG concentrations were related to HbA_{1c} more strongly than postprandial concentrations. However, a better correlation was observed between HbA_{1c} and mean daily glucose concentrations, confirming that HbA_{1c} is a function of both fasting and postprandial hyperglycemia (3). Although it seems from the results of previous studies (4,5) that postprandial hyperglycemia contributes to ~30–40% of the total daytime hyperglycemia, the debate remains wide open. The discrepancies between the data published over the last years seem to indicate that the answer to the question of the relative contribution of fasting and postprandial hyperglycemia to the overall diabetic disequilibrium might be more complex and subtle than expected. For instance, the magnitude of the relative contribution of postprandial glucose excursions to overall hyperglycemia might be influenced both by the circumstances under which blood glucose has been monitored in the postprandial period and by the degree of the overall diabetic control itself (1). The aim of the present study was to extend our knowledge on the latter point. For that purpose, we were led to analyze the diurnal glycemic profiles of non–insulin-using type 2 diabetic patients investigated at different levels of HbA_{1c}.

RESEARCH DESIGN AND METHODS

Patients

A total of 290 patients (139 men, 151 women) participated in the study and were entered consecutively. Eligibility for the study was based on a diagnosis of diabetes for at least 6 months. The subjects could be treated by diet alone or with a stable dose of metformin (1,700 mg/day),

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Abbreviations: AUC, area under the curve; AUC_1, AUC above fasting PG concentrations; AUC_2, AUC >6.1 mmol/l; CGMS, continuous glucose monitoring system; CV, coefficient of variation; PG, plasma glucose.

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

glyburide (5–15 mg/day), 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. Because insulin or acarbose treatments can or do exert specific effects on postprandial glucose excursions, patients who were being treated with acarbose or insulin were excluded to avoid any bias in the interpretation of the contribution of postprandial glucose increments to overall hyperglycemia. The study was conducted after the patients had given their informed consent. The patients were further divided into five equal groups according to the quintiles of HbA_{1c}. For that purpose, the 290 HbA_{1c} values were ranked in increasing order, with random ranking when two or several HbA_{1c} measurements were equal.

Protocol of the study

All patients were submitted to a protocol that has been previously described (6). After an overnight fast, all patients were admitted at the outpatient clinic of the Department of Metabolism, Lapeyronie Hospital. Patients were asked to eat a test breakfast at 8:00 A.M. and a test lunch at 12:00 P.M. The energy and macronutrient content of each test meal were standardized according to a dietary program, as previously described (6). Four venous blood samples were collected into tubes containing EDTA and fluoride at 8:00 A.M., 11:00 A.M., 2:00 P.M., and 5:00 P.M. Plasma was separated from the cells within <1 h after withdrawal, and glucose concentrations in plasma were determined by an hexokinase method using a Synchro CX4/CX5 glucose analyzer (Beckman Instruments, Fullerton, CA). Both the intra- and interassay coefficients of variation (CVs) were ≤2% at values <7 mmol/l. The rationale for the timing of the four PG determinations (i.e., of the so-called diurnal PG profiles) was initially determined by giving a priority choice to the two PG values that are usually considered to reflect a real fasting state (prebreakfast PG at 8:00 A.M.) and a nonquestionable postprandial period (2-h postlunch PG at 2:00 P.M.). The two remaining time points were chosen to respect a regular 3-h time interval between blood samplings. The 3-h postbreakfast PG at 11:00 A.M. can therefore be considered as a compromise between a late postbreakfast and an early prelunch value, whereas the 5-h postlunch PG value (extended postlunch at 5:00 P.M.) is a marker of a postabsorptive period (7,8). On the study day, patients were maintained on their usual treatment with oral antidiabetic drugs. HbA_{1c} measurement was made at 8:00 A.M. on the first blood sample by using a high-performance liquid chromatography assay (Menarini Diagnostics, Florence, Italy). The intra- and interassay CVs were <3% at values <8%.

Calculation of the relative contributions of fasting and postprandial plasma glucose to the overall hyperglycemia over the diurnal period of daytime

The diurnal PG response to meals was estimated as a whole by calculating the incremental area under the daytime PG curve from 8:00 A.M. to 5:00 P.M. Two areas were calculated geometrically from the four-point curve, the area below the baseline value being ignored. The first, the area under the curve (AUC) above fasting PG concentrations (AUC_1), 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, the AUC >6.1 mmol/l (AUC_2), was calculated above a baseline level equal to 6.1 mmol/l (110 mg/dl), reflecting the increases in both fasting and postprandial PG. The baseline value of 6.1 mmol/l was chosen because this threshold has been defined as the upper limit of normal PG at fasting or preprandial times by the American Diabetes Association (9,10). Therefore, the difference ($AUC_2 - AUC_1$) can be considered an assessment of the increment in fasting PG values. As a result, the relative contributions of postprandial and fasting PG to the total PG increment were calculated, respectively, by using the following equations: $(AUC_1/AUC_2) \times 100$ for the postprandial contribution and $[(AUC_2 - AUC_1)/AUC_2] \times 100$ for the fasting contribution.

Statistical analysis

All results are given as the mean ± SE. All data, particularly those concerning the relative contributions of fasting and postprandial PG to the total glucose increments, were compared over quintiles of HbA_{1c} by using one-way ANOVA, followed by a Bonferroni's test (11). Relative contributions of postprandial and fasting PG were compared by using a paired Student's *t* test. Correlation analyses were performed by using the least-square method, and strengths of the relationships were given by coefficients of determination (r^2).

Validation of the model using a four-point glucose profile

In the 290 patients, a significant correlation ($r^2 = 0.48$, $P < 0.0001$) was found between HbA_{1c} and AUC_2, this area integrating both fasting and postprandial glucose increments and being considered a reflection of the average exposure to high glucose over the diurnal period of the study day. Furthermore, to know more precisely whether the areas calculated from the four–time point diurnal glucose profiles provide an objective reflection of variations in fasting and postprandial glucose levels during real life, we investigated an additional subgroup of 20 type 2 diabetic patients who were selected according to the same criteria as the 290 patients included in the study. The values (mean ± SE) in this subgroup were 62.4 ± 1.2 years for age, 10.3 ± 0.9 years for diabetes duration, 30.2 ± 0.6 kg/m^2 for BMI, and 8.77 ± 0.26% for HbA_{1c}. In the 20 patients, the subcutaneous interstitial glucose level was monitored on an ambulatory basis and over 24 h using the Minimed continuous glucose monitoring system (CGMS; Northridge, CA) (12,13). The glucose patterns as obtained were submitted to the following readings and calculations, which are illustrated in Fig. 1. First, for each patient, four glucose values were read on the time curves at 8:00 A.M., 11:00 A.M., 2:00 P.M., and 5:00 P.M. The four time points were connected by straight lines over time, and then trapezoidal areas were calculated from 8:00 A.M. to 5:00 P.M. according to the method as described above. These areas were termed as AUC_1 4-pt, AUC_2 4-pt, and ($AUC_2 - AUC_1$) 4-pt. Second, incremental areas under continuous glucose monitoring were calculated from the CGMS patterns both over the diurnal 9-h period (from 8:00 A.M. to 5:00 P.M.) and over 24 h. These areas were termed AUCs 9-h and AUCs 24-h. Areas under continuous glucose monitoring were determined by dividing the entire daytime period into three periods, each starting with the main meals (breakfast, lunch, and dinner) and ending with the subsequent meal. Over each period, AUC_1s continuous were defined as the incremental areas above pre-

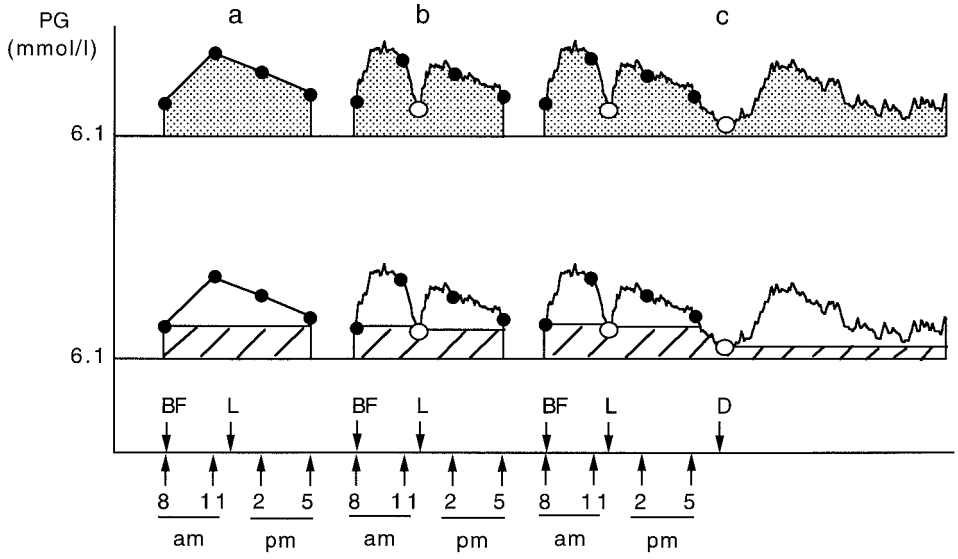

Figure 1—*Description in a typical patient of the calculations used for determining the incremental AUCs of glucose.* a*: Diurnal four-point profiles.* b*: Diurnal 9-h continuous profile.* c*: 24-h continuous profile. BF, breakfast; D, dinner; and L, lunch. Measurements were respectively taken at 8:00 A.M., 12:00 P.M., and 7:00 P.M. AUC_1: white areas (lower part of the figure); AUC_2: shaded areas (upper part of the figure). $AUC_2 - AUC_1$: hatched areas (lower part of the figure). ●, values transcribed from the CGMS pattern for establishing the four-point profile and prebreakfast values; ○, preprandial values before lunch and dinner.*

prandial glucose values that were read just before starting breakfast, lunch, and dinner. AUC_1s 9-h and 24-h were calculated by summing the areas up to 5:00 P.M. and over 24 h, respectively. AUC_2s 9-h and 24-h were measured by calculating the total areas under the CGMS values >6.1 mmol/l. The differences in $AUC_2 - AUC_1$ were calculated and termed as ($AUC_2 - AUC_1$) 9-h and 24-h.

In the 20 patients, highly significant correlations were found between AUC_2 4-pt and either AUC_2 9-h over the diurnal period ($r^2 = 0.93$, $P < 0.0001$) or AUC_2 24-h ($r^2 = 0.82$, $P < 0$ 0.0001). Less significant correlations were observed between AUC_1 4-pt and either AUC_1 9-h ($r^2 = 0.40$, $P = 0.002$) or AUC_1 24-h ($r^2 = 0.21$, $P = 0.041$). However, correlations remained highly significant when ($AUC_2 - AUC_1$) 4-pt was tested against either ($AUC_2 - AUC_1$) 9-h ($r^2 = 0.89$, $P < 0.0001$) or 24-h ($r^2 = 0.86$, $P < 0.0001$).

Evaluation of glucose stability over the prebreakfast period

Because prebreakfast glucose values were used as reference for estimating the "real" fasting state and therefore served for evaluating the fasting and postprandial glucose increments, we calculated the CV of glucose fluctuations obtained from the CGMS over the 30-min interval that preceded the starting glucose level before breakfast. For each of the 20 patients, individual means and CVs were calculated by averaging seven glucose values that were obtained from 5-min interval readings over the 30-min prebreakfast period. The mean within-subject CV for the 20 patients was further calculated from the individual data and was estimated at 5.1%.

RESULTS

Main clinical data and diurnal plasma glucose profiles

All results are indicated in Table 1 and Fig. 2. As expected, all PG values both at fasting and during postprandial or postabsorptive periods were increasing significantly and progressively from the lowest to the highest quintiles of HbA_{1c}.

Relative contributions of fasting and postprandial glucose to the overall diurnal hyperglycemia

The values of AUC_1 and AUC_2 are given in Fig. 2 with the differences ($AUC_2 - AUC_1$). AUC_1, which reflects postprandial glucose increments, was significantly decreased in the lowest quintile of HbA_{1c} when compared with all of the remaining quintiles. The AUC_1 value exhibited a threefold increase from quintile 1 to 3, reached a quasi-plateau at quintile 3, and remained stable over quintiles 4 and 5. The difference ($AUC_2 - AUC_1$), which reflects fasting glucose increments, increased progressively with increasing levels of HbA_{1c}, with significant differences being found between each quintile taken individually and all of the following upper quintiles.

As shown in Fig. 3, the relative contribution of postprandial PG decreased progressively from the lowest to the highest quintile of HbA_{1c}. By contrast, the relative contribution of fasting PG showed a gradual increase with increasing levels of HbA_{1c}.

For each relative postprandial or fast-

Table 1—*Clinical data*

Quintiles of HbA_{1c}	1	2	3	4	5	Entire population
Patients tested (*n*)	58	58	58	58	58	290
Sex ratio (M/F)	31/27	34/24	22/36	27/31	25/33	139/151
Age (years)	62.6 ± 1.1	56.5 ± 1.4	62.3 ± 1.3	60.7 ± 1.3	58.3 ± 1.4	60.1 ± 0.6
Diabetes duration (years)	8.4 ± 1.3	10.0 ± 1.1	13.8 ± 1.7	11.7 ± 1.2	8.3 ± 1.1	10.5 ± 0.6
BMI (kg/m^2)	30.6 ± 0.8	31.7 ± 0.9	29.9 ± 0.7	30.3 ± 0.9	29.6 ± 0.8	30.4 ± 0.4
HbA_{1c} (%)	6.45 ± 0.08	7.93 ± 0.04	8.85 ± 0.03	9.76 ± 0.04	11.32 ± 0.13	8.86 ± 0.10

Data are means ± SE.

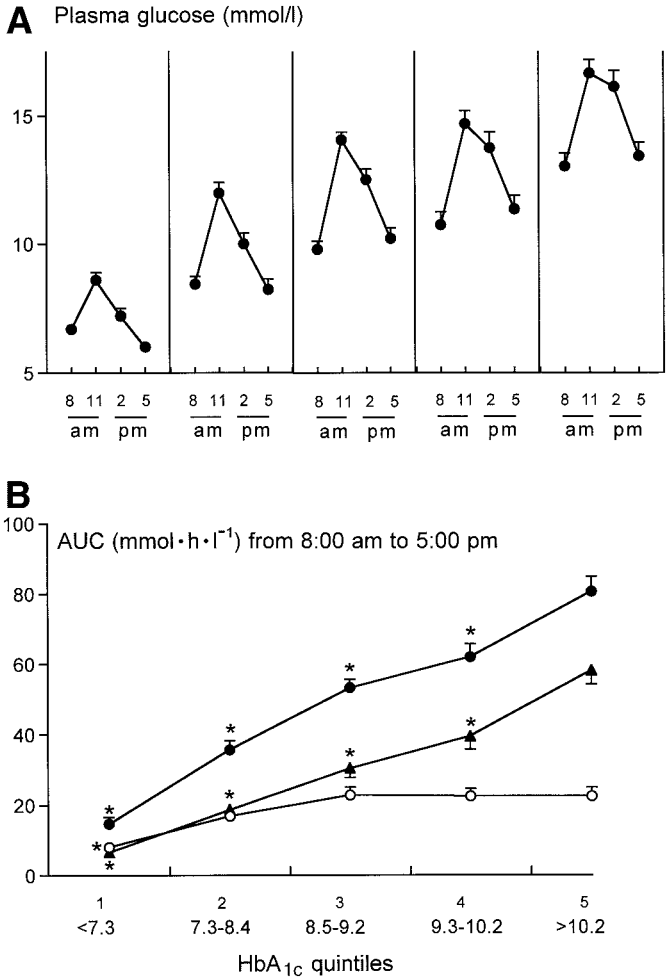

Figure 2—*Four–time point diurnal profiles of plasma glucose concentrations* (A) *and AUCs* (B) *over quintiles of HbA_{1c}. ○, AUC_1; ●, AUC_2; ▲, $AUC_2 - AUC_1$ (differences between the two areas). Methods of calculation and meanings for each area are provided in the text; and results are given as the means ± SE. *Significant differences from all following upper quintiles. All* P *values are <0.001 after Bonferroni adjustment, except for comparisons between quintiles 1 and 2 of AUC_1* (P = *0.015) or $AUC_2 - AUC_1$* (P = *0.032) and between quintiles 2 and 3* (P = *0.047) of $AUC_2 - AUC_1$.*

ing contribution, analyzed individually, comparisons over quintiles of HbA_{1c} showed significant differences first between the lowest quintile and all of the following upper quintiles, and second between the 2nd and the 5th quintile. Furthermore, significant differences were found in quintiles 1, 4, and 5 when relative postprandial and fasting contributions were compared within the same quintile.

In the 20 patients investigated with the CGMS, the relative contributions of postprandial glucose to the overall hyperglycemia, as estimated from the ratios of AUC_1 9-h to AUC_2 9-h and AUC_1 24-h to AUC_2 24-h, were negatively correlated with HbA_{1c} levels, but the relationship was only significant ($r^2 = 0.40$, $P = 0.002$) for the contribution over 24 h. As expected, $[(AUC_2 - AUC_1)/AUC_2]$ 9-h and 24-h correlated with HbA_{1c} at the same level of significance, but in a positive manner.

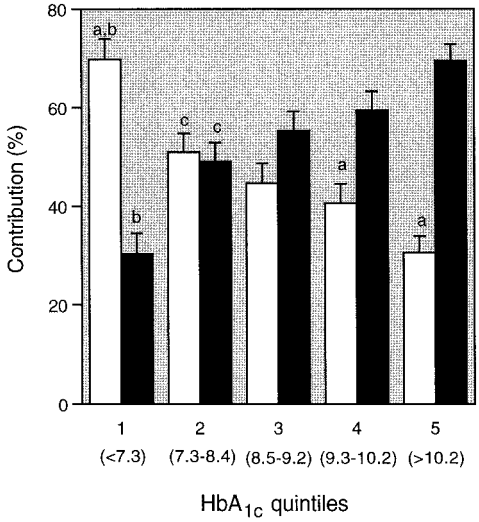

Figure 3—*Relative contributions of postprandial (□) and fasting (■) hyperglycemia (%) to the overall diurnal hyperglycemia over quintiles of HbA_{1c}.* a, *significant difference was observed between fasting and postprandial plasma glucose (paired* t *test);* b, *significantly different from all other quintiles (ANOVA);* c, *significantly different from quintile 5 (ANOVA).*

CONCLUSIONS — The present results suggest that postprandial glycemic excursions play a major role in the metabolic disequilibrium of patients suffering from mild or moderate hyperglycemia. On the contrary, fasting hyperglycemia appears as a main contributor to the overall diurnal hyperglycemia in poorly controlled diabetic patients, whereas the role of postprandial glucose elevations decreases as patients progress toward poor diabetic control. Because this relationship was confirmed in the 20 patients investigated with the CGMS, all periods that are not accounted for in the four–time point glucose profile do not seem to affect the validity of the results given by our four-point sampling model, which integrates markers during the three main (fasting, postprandial, and postabsorptive) periods of daytime.

The importance of postprandial glycemic excursions in fairly well-controlled type 2 diabetic patients is in agreement with the results of all epidemiological studies (14,15), which have shown that postchallenge hyperglycemia was a stronger predictor of cardiovascular disease than elevation of glucose at fasting. However, these findings were solely observed in diabetic patients with mild or moderate alterations of diabetic control and mostly in subjects who were only suffering from

impaired tolerance to glucose (15). On the contrary, fasting hyperglycemia plays a major role as soon as the HbA_{1c} level rises above 8.4%. This finding results mainly from the fact that $AUC_2 - AUC_1$ (a reflection of fasting glucose exposure) increased steadily from quintile 1 to 5, whereas AUC_1 (a reflection of postprandial exposure) remained stable over the three upper quintiles. These observations are consistent with U.K. Prospective Diabetes Study data (16), which have provided cogent evidence for the deleterious effect of fasting hyperglycemia in the progression and development of vascular complications in patients suffering from overt diabetes with frank elevations of glucose values at fasting. However, even in this type of patient, the role of postprandial glycemic excursions remains possible because in the quintile of our patients who had the highest levels of HbA_{1c}, postprandial hyperglycemia accounted for approximately one-fourth of the total diurnal hyperglycemia. Such an observation can explain the specific deleterious effect of postprandial hyperglycemia as reported in the subset of poorly controlled type 2 diabetic patients who were included in the Diabetes Intervention Study (17).

All of these interpretations are tenable, provided that the validity of the observations on a four–time point diurnal glucose profile in standard conditions with standardized meals on a specific study might be extended to the chronic variations of plasma glucose in real life. An answer to refute all these possible limitations is given by the finding of significant correlations between the areas under the four–time point diurnal glucose profiles and several parameters, such as HbA_{1c} measurements, which usually evaluate the chronic variations of plasma glucose (18), and the incremental areas with the CGMS data, which provide information on continuous changes of glucose levels in real life. These findings are in accordance with our a priori hypothesis that the areas calculated from the four–time point profiles can be used as a proxy for the areas under both diurnal and 24-h continuous glucose monitoring. Furthermore, the intraindividual variability of the prebreakfast glucose values that served as a reference for determinations of AUCs seems to be sufficiently reduced (CV = 5.1%) for meaningful interpretation of the data, since this relatively small imprecision in fasting PG is compensated by the size of the investigated population.

In conclusion, our results indicate that there exists a progressive shift in the respective contributions of fasting and postprandial hyperglycemia when the patients progress from moderate to high hyperglycemia, the contribution of postprandial glucose excursions being predominant in patients with moderate diabetes, whereas the contribution of fasting hyperglycemia increases with diabetes worsening. Such observations seem to conciliate the different results that were observed in the literature because the shift in the respective contributions of fasting and postprandial hyperglycemia appears as a continuous spectrum from fairly to poorly controlled patients with type 2 diabetes.

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