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

Variations with increasing levels of HbA1c

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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 HbA1c.

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 (AUC1) and >6.1 mmol/l (AUC2) were calculated for further evaluation of the relative contributions of postprandial (AUC1/AUC2, %) and fasting [(AUC2 − AUC1)/AUC2, %] PG increments to the overall diurnal hyperglycemia. The data were compared over quintiles of HbA1c.

RESULTS — The relative contribution of postprandial glucose decreased progressively from the lowest (69.7%) to the highest quintile of HbA1c (30.5%, P < 0.001), whereas the relative contribution of fasting glucose increased gradually with increasing levels of HbA1c: 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.
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 HbA1c. For that purpose, the 290 HbA1c values were ranked in increasing order, with random ranking when two or several HbA1c 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 cose concentrations in plasma were determined by giving a priority choice to the two PG values that are usually considered as a compromise between a late postprandial 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. HbA1c 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 (AUCf), 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 of fasting PG (AUCf), 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 prepandial times by the American Diabetes Association (9,10). Therefore, the difference (AUCf − AUCf) 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: (AUCf/AUCf) × 100 for the postprandial contribution and [(AUCf − AUCf)/AUCf] × 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 HbA1c 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).

**Validation of the model using a four-point glucose profile**

In the 290 patients, a significant correlation (r² = 0.48, P < 0.0001) was found between HbA1c and AUCf, 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/m² for BMI, and 8.77 ± 0.26% for HbA1c. 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 AUCf 4-pt, AUCf 4-pt, and AUCf − AUCf 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, AUCs 9-h continuous were defined as the incremental areas above pre-
prandial glucose values that were read just before starting breakfast, lunch, and dinner. AUC\textsubscript{1S} 9-h and 24-h were calculated by summing the areas up to 5:00 P.M. and over 24 h, respectively. AUC\textsubscript{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\textsubscript{2} — AUC\textsubscript{1} were calculated and termed as (AUC\textsubscript{2} — AUC\textsubscript{1}) 9-h and 24-h.

In the 20 patients, highly significant correlations were found between AUC\textsubscript{2} 4-pt and either AUC\textsubscript{2} 9-h over the diurnal period ($r^2 = 0.93, P < 0.0001$) or AUC\textsubscript{2} 24-h ($r^2 = 0.82, P < 0.0001$). Less significant correlations were observed between AUC\textsubscript{1} 4-pt and either AUC\textsubscript{1} 9-h ($r^2 = 0.40, P = 0.002$) or AUC\textsubscript{1} 24-h ($r^2 = 0.21, P = 0.041$). However, correlations remained highly significant when (AUC\textsubscript{2} — AUC\textsubscript{1}) 4-pt was tested against either (AUC\textsubscript{2} — AUC\textsubscript{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\textsubscript{1c}.

Table 1—Clinical data

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

Data are means ± SE.

Relative contributions of fasting and postprandial glucose to the overall diurnal hyperglycemia
The values of AUC\textsubscript{1} and AUC\textsubscript{2} are given in Fig. 2 with the differences (AUC\textsubscript{2} — AUC\textsubscript{1}). AUC\textsubscript{1}, which reflects postprandial glucose increments, was significantly decreased in the lowest quintile of HbA\textsubscript{1c} when compared with all of the remaining quintiles. The AUC\textsubscript{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\textsubscript{2} — AUC\textsubscript{1}), which reflects fasting glucose increments, increased progressively with increasing levels of HbA\textsubscript{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\textsubscript{1c}. By contrast, the relative contribution of fasting PG showed a gradual increase with increasing levels of HbA\textsubscript{1c}.

For each relative postprandial or fast-
ing contribution, analyzed individually, comparisons over quintiles of HbA1c 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 AUC1 9-h to AUC2 9-h and AUC1 24-h to AUC2 24-h, were negatively correlated with HbA1c levels, but the relationship was only significant ($r^2 = 0.40, P = 0.002$) for the contribution over 24 h. As expected, $[(\text{AUC}_2 - \text{AUC}_1)/\text{AUC}_1]$ 9-h and 24-h correlated with HbA1c at the same level of significance, but in a positive manner.

**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 mild or moderate hyperglycemia.
impaired tolerance to glucose (15). On the contrary, fasting hyperglycemia plays a major role as soon as the HbA1c 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$_4$ (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 HbA1c, 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 HbA1c 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 precision 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.

References