Impact of postprandial and fasting glucose concentrations on HbA1c in patients with type 2 diabetes

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Abstract

Aim. – This study aimed to assess the relative contributions of postprandial and fasting glucose concentrations to overall hyperglycaemia.

Methods. – Patients with type 2 diabetes (n = 973) carried out self-monitored blood glucose (SMBG) profiles on entry into the European Exenatide (EUREXA) trial. Glucose area under the curve was calculated for postprandial excursions (AUCppg) and total daytime concentrations > 6.1 mmol/L (AUCTotal), as well as for the percentage of glycaemia due to postprandial excursions (%ppg). In addition, OGTT scores were assessed for each patient. Results were evaluated according to defined HbA1c categories.

Results. – There was a significant linear relationship between HbA1c and the derived variables of AUCppg, AUCTotal and %ppg (P < 0.001 for each), with explained variance greatest for AUCTotal (r² = 37.4%). AUCppg increased only slightly up to an HbA1c of 7.0%, but showed a steeper increase in higher HbA1c categories. Also, the increase in AUCTotal with increasing HbA1c was much more pronounced. As a result, the postprandial glucose excursion as a proportion of total glucose (%ppg) decreased across HbA1c categories from 61.0% at HbA1c < 6.5% to 22.0% at HbA1c ≥ 9.0%. HOMA-IR remained virtually unchanged through all HbA1c categories, while HOMA-B showed no large changes up to HbA1c 7.0%, but then decreased at higher HbA1c values. The Δ130/ΔG30 ratio decreased in the HbA1c 7.0–7.9% category, but did not change greatly at higher HbA1c categories.

Conclusion. – With increasing HbA1c, there was a decrease in the contribution of postprandial hyperglycaemia to total glycaemia, and fasting hyperglycaemia became more important. This is consistent with impaired insulin release, particularly first-phase release, at higher HbA1c levels.

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Keywords: Type 2 diabetes; Postprandial hyperglycaemia; Fasting hyperglycaemia; Beta-cell function; Insulin resistance; HbA1c

Résumé

Impact de la glycémie postprandiale sur le taux d’HbA1c des patients diabétiques de type 2.

Objectif. – Déterminer la contribution relative des glycémies postprandiales et des glycémies à jeun dans l’hyperglycémie totale, évaluée par le taux d’HbA1c.

Méthodes. – Lors de l’inclusion dans l’étude européenne exenatide (EUREXA), les patients atteints d’un diabète de type 2 (DT2) (n = 973), ont effectué un autocontrôle glycémique (SMBG). Les variables suivantes ont été calculées: aire sous la courbe des excursions glycémiques postprandiales (AUCppg) et des excursions glycémiques journalières totales supérieures à 6,1 mmol/l (AUCTotal), ainsi que le pourcentage d’hyperglycémie liée aux excursions postprandiales (%ppg). En outre, une hyperglycémie provoquée orale (HGPO) a été réalisée chez chaque patient. Les résultats ont été évalués en fonction de classes d’HbA1c prédéfinies.
1. Introduction

Type 2 diabetes mellitus is characterized by progressive deterioration of beta-cell function [1–3], with a steady decline in glucose control [4]. The initial stage of this process—a decline in insulin action coupled with defects in early-phase insulin secretion [5,6]—occurs before clinical manifestation of the disease. These abnormalities are responsible for the initial change from normal to impaired glucose tolerance and eventually lead to overt diabetes. This means that type 2 diabetes is initially a disorder of postprandial glucose control. It has been shown that postprandial glucose increments are the predominant contributor to worsening diabetes [7]. The relative contributions of fasting glucose and postprandial excursions to overall hyperglycaemia have been quantified in patients at various levels of HbA1c, using a four-point daytime glucose profile [7]. In a subsequent study [8], 24-h glucose profiles from continuous glucose monitoring were measured in patients on diet treatment alone, or on diet plus oral antidiabetic drugs. The results showed that the first significant increment in postprandial hyperglycaemia occurred when going from HbA1c < 6.5% to HbA1c 6.5–6.9%, followed by further stepwise increments in fasting daytime and nocturnal hyperglycaemia at higher HbA1c levels. The implication from these and other studies [9–11] is that control of fasting hyperglycaemia alone is not enough to achieve HbA1c levels < 7.0% in type 2 diabetes patients and that initial treatment should specifically target the control of postprandial hyperglycaemia.

The present study assessed the contributions of postprandial and fasting glucose levels in patients with type 2 diabetes who had been previously treated with diet and exercise, followed by metformin treatment. The present analysis used the methods of Monnier et al. [7] to quantify the relative contributions of fasting and postprandial glucose excursions to overall hyperglycaemia, based on self-monitored blood glucose (SMBG). All study patients had undergone assessment of beta-cell function as part of a treatment intervention study protocol, and their available data were evaluated in relation to fasting and postprandial glucose control.

2. Research design and methods

2.1. Patients

Analyses were carried out using baseline data from patients with type 2 diabetes recruited into the European Exenatide (EUREXA) randomized, open-label, multicentre trial of add-on treatment with either exenatide or sulphonylurea after metformin failure. Patients were aged 18–85 years with body mass index (BMI) scores ≥ 25 kg/m², but ≤ 40 kg/m², and had been taking a stable, maximum-tolerated dose of immediate- or extended-release metformin for at least 3 months. Patients with symptomatic retinopathy, hepatic or gastrointestinal disease, renal failure or active malignancy, or who had previously been treated with thiazolidinediones, insulin, alpha-glucosidase inhibitors, sulphonylurea or meglitinides, were excluded from the study. For the present analyses, all randomized patients with baseline SMBG measurements and baseline HbA1c ≥ 6.0%, but ≤ 10.0%, were evaluated: a total of 973 out of 1039 randomized patients from 12 countries fulfilled these criteria. The study was carried out with the appropriate ethics review board approvals, and all patients signed an informed consent document.

2.2. Study evaluations

SMBG profiles included sampling before and 2 h after the morning, midday and evening meals, and at 0300 h; however, for calculation of derived variables, only the first six time points (prebreakfast to 2 h after dinner) were evaluated. As with Monnier et al. [7], daytime postprandial hyperglycaemia excursions (AUCppg) were calculated using the glucose area above the prebreakfast glucose concentration, while total hyperglycaemia (AUCtotal) was calculated using the glucose area above 6.1 mmol/L. The percentage of hyperglycaemia due to postprandial excursions (%ppg) was calculated as: (AUCppg ÷ AUCtotal) × 100%. To calculate AUCppg and AUCtotal, it was assumed that the pre- and postbreakfast, -lunch and -dinner measurements occurred at 0800, 1000, 1200, 1400, 1800 and 2000 h, respectively, although the actual times were more variable. In addition, all patients underwent a standardized oral glucose tol-
Table 1
Demographic and clinical data of the study patients.

<table>
<thead>
<tr>
<th>HbA1c category</th>
<th>&lt;6.5% (n = 35)</th>
<th>6.5–6.9% (n = 246)</th>
<th>7.0–7.9% (n = 461)</th>
<th>8.0–8.9% (n = 212)</th>
<th>≥9.0% (n = 19)</th>
<th>Total (n = 973)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)²</td>
<td>59.9 ± 9.4</td>
<td>57.6 ± 9.8</td>
<td>57.2 ± 9.6</td>
<td>55.1 ± 9.5</td>
<td>55.1 ± 8.5</td>
<td>56.9 ± 9.6</td>
</tr>
<tr>
<td>Female/male (%/%)</td>
<td>45.7/54.3</td>
<td>48.8/51.2</td>
<td>47.3/52.0</td>
<td>40.6/59.4</td>
<td>57.9/42.1</td>
<td>46.4/53.6</td>
</tr>
<tr>
<td>BMI (kg/m²)²</td>
<td>31.0</td>
<td>32.0 ± 4.2</td>
<td>32.5 ± 4.0</td>
<td>32.7 ± 3.9</td>
<td>34.8 ± 4.7</td>
<td>32.4 ± 4.1</td>
</tr>
<tr>
<td>Duration of diabetes (years)²</td>
<td>4.6 ± 4.0</td>
<td>5.1 ± 4.4</td>
<td>5.7 ± 4.7</td>
<td>6.1 ± 4.5</td>
<td>6.1 ± 3.7</td>
<td>5.6 ± 4.6</td>
</tr>
<tr>
<td>Daily metformin dose (mg)²</td>
<td>1876 ± 637</td>
<td>1946 ± 612</td>
<td>1948 ± 629</td>
<td>2005 ± 587</td>
<td>2255 ± 555</td>
<td>1963 ± 615</td>
</tr>
<tr>
<td>Patients with hypertension (%)</td>
<td>31.4</td>
<td>35.4</td>
<td>30.4</td>
<td>30.2</td>
<td>31.6</td>
<td>31.7</td>
</tr>
<tr>
<td>Patients on lipid medication (%)</td>
<td>45.7</td>
<td>48.8</td>
<td>47.3</td>
<td>40.6</td>
<td>57.9</td>
<td>46.4</td>
</tr>
<tr>
<td>Patients on β-blockers (%)</td>
<td>30.2</td>
<td>30.4</td>
<td>30.2</td>
<td>30.2</td>
<td>30.2</td>
<td>30.2</td>
</tr>
</tbody>
</table>

² Means ± SD.

Diabetic control was assessed using the glycated haemoglobin (HbA1c) (Volu-Mark, Biorey, Munich, Germany). Plasma glucose was measured by a hexokinase method (COBAS Gluco-quant, Roche Diagnostics GmbH, Mannheim, Germany) and insulin by a two-site chemiluminescence immunoassay (IMMULITE 2000, Siemens Diagnostics, Tarrytown, NY, USA).

2.3. Statistical analysis

As in the study by Monnier et al. [8], patients were subdivided into the following HbA1c categories: <6.5%; 6.5–6.9%; 7.0–7.9%; 8.0–8.9%; and ≥9.0%. Results according to these five HbA1c categories were presented as means and standard deviations (SD), with interquartile ranges (Q1–Q3) where appropriate, or as medians with interquartile ranges where data were skewed. Exploratory regression analyses were used to examine the linear relationship between HbA1c concentration and daily metformin dose, HbA1c concentration and the derived variables of AUCppg, AUCtotal and %ppg, as well as HbA1c concentration vs HOMA-B, HOMA-IR, ΔI30/ΔG30 and the disposition index. Also, regression analyses were performed on ranked data in case the normality assumption did not hold.

3. Results

Patients’ demographic and clinical data (Table 1), according to HbA1c categories, showed that duration of diabetes and daily metformin dose increased progressively from lower to higher HbA1c values. There was a statistically significant linear relationship between HbA1c and daily metformin dose (P = 0.0002). In addition, although the average daily SMBG profiles in the five HbA1c groups (Table 2) shifted progressively upwards, the first pronounced increase was only seen above the 7.0–7.9% HbA1c category. For the <6.5% and 6.5–6.9% categories, the highest mean postprandial glucose concentrations were 7.8 ± 1.8 mmol/L and 8.3 ± 1.7 mmol/L, respectively, with an increase of up to 9.5 ± 2.0 mmol/L in the 7.0–7.9% HbA1c category. The lower premeal glucose quartile (Q1) in the two lowervest HbA1c categories ranged from 5.0 to 6.6 mmol/L, and the postprandial Q1 glucose ranged from 4.4 to 7.1 mmol/L, indicating that almost one-fourth of the patients in these groups did not have hyperglycaemic values when tested.

The derived variables AUCppg, AUCtotal and percentage of hyperglycaemia due to postprandial glucose elevation (%ppg) were plotted by HbA1c categories (Fig. 1). Regression analyses showed a significant linear relationship between HbA1c concentration and these derived variables (P < 0.001 for each). However, the explained variance in HbA1c was much greater for AUCtotal (r² = 37.4%) than for either AUCppg (r² = 4.9%) or %ppg (r² = 5.3%). The increase in AUCppg from HbA1c category <6.5% to 6.5–6.9% was limited (from 7.1 ± 7.1 to 7.4 ± 7.2 mmol/L), whereas the steeper increase (up to 9.3 ± 8.2 mmol/L) was seen at HbA1c 7.0–7.9%. The pattern of AUCtotal was similar, albeit more continuous and steeper, with the increase from HbA1c 6.5% to 6.5–6.9% being more pronounced (13.3 ± 10.7 mmol/L and 17.5 ± 10.8 mmol/L, respectively), whereas the increases seen in the higher HbA1c

Fig. 1. Calculated mean areas under the curve for self-monitored total daytime glucose (AUCtotal), postprandial excursions (AUCppg), mean relative contribution of AUCppg to AUCtotal (%ppg) and upper limit of the 95% confidence interval, according to the HbA1c category of patients with type 2 diabetes.
Table 2

<table>
<thead>
<tr>
<th>HbA1c Category</th>
<th>Before breakfast</th>
<th>At 2 h after breakfast</th>
<th>Before lunch</th>
<th>At 2 h after lunch</th>
<th>Before dinner</th>
<th>At 0300 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt; 6.5%</td>
<td>6.9 ± 0.9</td>
<td>6.4–7.4</td>
<td>7.6 ± 1.6</td>
<td>6.7–9.3</td>
<td>6.4 ± 1.4</td>
<td>5.6–6.9</td>
</tr>
<tr>
<td>HbA1c 6.5–6.9%</td>
<td>7.6 ± 1.8</td>
<td>7.1–7.9</td>
<td>8.2 ± 1.5</td>
<td>7.3–9.7</td>
<td>8.9 ± 2.4</td>
<td>7.6–8.7</td>
</tr>
<tr>
<td>HbA1c 7.0–7.9%</td>
<td>8.0 ± 1.7</td>
<td>7.5–8.5</td>
<td>9.1 ± 2.2</td>
<td>8.7–10.9</td>
<td>10.8 ± 2.7</td>
<td>8.9 ± 1.3</td>
</tr>
<tr>
<td>HbA1c 8.0–8.9%</td>
<td>8.5 ± 2.2</td>
<td>7.9–9.5</td>
<td>9.6 ± 1.9</td>
<td>9.1–11.2</td>
<td>11.9 ± 2.7</td>
<td>9.9 ± 1.2</td>
</tr>
<tr>
<td>HbA1c ≥ 9.0%</td>
<td>9.1 ± 2.8</td>
<td>8.5–9.9</td>
<td>9.2 ± 2.4</td>
<td>9.7–11.4</td>
<td>11.3 ± 2.8</td>
<td>10.6 ± 3.0</td>
</tr>
</tbody>
</table>

Fig. 2. Mean and upper limit of the 95% confidence interval for HOMA-B, HOMA-IR and the \( \Delta I_{30}/\Delta G_{30} \) ratio from OGTT, according to the HbA1c category of patients with type 2 diabetes.

categories ranged from two-fold to more than five-fold. As a result of these concomitant changes, the calculated percentage of total glucose area contributed by postprandial glucose excursions (%ppg) decreased across all five HbA1c groups — from 61.0% at HbA1c < 6.5% to 22.0% at HbA1c ≥ 9.0%.

In Fig. 2, the values for HOMA-B, HOMA-IR and the \( \Delta I_{30}/\Delta G_{30} \) ratio are presented according to HbA1c categories. HOMA-B was almost unchanged from HbA1c < 6.5% to 6.5–6.9% (70.5 ± 48.8 to 75.9 ± 74.6), but decreased with higher HbA1c values to 40.0 ± 24.4 at HbA1c ≥ 9.0%. There was also a statistically significant linear relationship between HbA1c and HOMA-B (\( P < 0.001 \)), with an explained variance of 3.9%. As for the \( \Delta I_{30}/\Delta G_{30} \) ratio, it decreased from 39.6 ± 27.6 to 29.4 ± 45.1 pmol/mmol between the HbA1c < 6.5% group and the 6.5–6.9% group, with further decreases in HbA1c 8.0–8.9% (17.2 ± 16.9 pmol/mmol), but little change at the highest HbA1c level. Regression analyses of the relationship between HbA1c concentrations and the insulinogenic index (\( \Delta I_{30}/\Delta G_{30} \)) showed a statistically significant linear relationship (\( P < 0.001 \)) with an explained variance of 4.8%.

In contrast, although the linear relationship between HbA1c concentrations and HOMA-IR was statistically significant (\( P < 0.001 \), explained variance 1.2%), the HOMA-IR changed little with increasing HbA1c — from 6.4 ± 7.5 at HbA1c < 6.5% to 6.5 ± 4.3 at HbA1c 8.0–8.9% and to 8.2 ± 3.7 at HbA1c ≥ 9.0%.

The median (Q1–Q3) disposition indices for the HbA1c categories were 7.0 (4.4–14.7), 5.2 (3.2–9.6), 3.8 (2.2–6.2), 2.6 (1.4–4.4) and 1.9 (1.0–2.2) for HbA1c < 6.5%, 6.5–6.9%, 7.0–7.9%, 8.0–8.9% and > 9.0%, respectively, and the decrease in disposition index (ranked data) with increasing HbA1c was statistically significant (\( P < 0.001 \)), with an explained variance of 13.7%.
4. Discussion

In the present study, we used the method proposed by Monnier et al. [7] to evaluate the relative contributions of postprandial and fasting hyperglycaemia to overall daytime glucose control in a large patient population with type 2 diabetes and experiencing inadequate glucose control with metformin treatment. In that study, postprandial and fasting glucose levels were originally stratified from an HbA1c of 7.3%, using a four-point glucose profile [7]. In a subsequent report, the stepwise deterioration of postprandial glucose control allowed stratification of patients from an HbA1c < 6.5%, and comparison of mean glucose concentrations during nocturnal fasting, and morning and daytime postprandial periods, using 24-h continuous glucose monitoring [8]. The present study design also used stratification from an HbA1c < 6.5% onwards, and analyzed a six-point SMBG daytime profile in patients who were not following a standardized dietary intake, but receiving metformin treatment instead; it should be noted, however, that there were fewer patients in the lowest (n = 35) and highest (n = 19) HbA1c categories than in the intermediate HbA1c categories.

The present study also differs from that of Monnier et al. [8] in that it was a cross-sectional evaluation of a larger and more homogeneous population of patients who had developed suboptimal glucose control after previous treatment with metformin. Additional assessments in the present study included the relationship of HbA1c with beta-cell function and insulin resistance. However, despite these differences and limitations, our data confirm that, with increasing HbA1c, the contribution of fasting hyperglycaemia relative to postprandial hyperglycaemia is also progressively increased, with the more relevant changes seen at HbA1c levels > 7.0%, when morning fasting glucose exceeded 6.1 mmol/L in the majority of patients. At the lower HbA1c categories of < 6.5% and 6.5–6.9%, glucose control ranged from normal/near-normal to initial impairment, indicated by the interquartile range of glucose values in these two HbA1c categories: when fasting values approached or were < 6.1 mmol/L, the AUCtotal was close to 0. If the same patients showed a postprandial glucose < 7.8 mmol/L, the %ppg formula reflected the magnitude of postprandial glucose values rather than a hyperglycaemic event.

Using continuous glucose monitoring, Monnier et al. [8] showed that the first step in the deterioration of glycaemic control in type 2 diabetes was an increase in daytime postprandial glycaemia at HbA1c levels > 6.5%, when patients with near-normal prebreakfast glucose values progressively exhibited abnormal rises in glucose levels after meals. Accordingly, patients in the two lower HbA1c categories covered the range of initial deterioration of glucose control. Thus, our results are, despite the different study design and limited precision of SMBG assessment, consistent with those obtained by Monnier et al. with continuous glucose monitoring. In addition, our data from the OGTT extend the previous observations and provide further evidence of progressive impairment of beta-cell function in type 2 diabetes.

HOMA-IR, a measure of insulin sensitivity, remained relatively constant across all HbA1c categories, while HOMA-B, a measure of beta-cell function, was initially stable and only began to decrease from HbA1c > 7.0% onwards. In contrast, the ΔI30/ΔG30 ratio, considered to represent first-phase insulin release, decreased with increasing HbA1c from the lowest categories on up. It has already been demonstrated that the early-phase response after oral glucose ingestion is an important determinant of the subsequent increment in plasma glucose [12]. Thus, the ΔI30/ΔG30 decrease in the lower HbA1c categories is consistent with impairment of insulin release as the initial stage in the natural decline of beta-cell function in patients with type 2 diabetes, and was even more evident when adjusted for insulin resistance as the disposition index. In our study patients, the decrease in HOMA-B, which is derived from fasting glucose values and reflects basal insulin release, was seen at HbA1c levels > 7.0% in parallel with the second step towards deterioration of glycaemic control found by Monnier et al. [8], including the period corresponding to the dawn phenomenon.

All patients in the present study were receiving metformin treatment, frequently the first-choice oral antidiabetic agent, as it improves glycaemic control primarily by sensitizing the liver to the effects of insulin [16,17]. Also, HOMA-IR data suggest that the drug is similarly effective across all HbA1c categories, as insulin resistance changed only slightly with increasing HbA1c. The patients included in the study were recruited on the basis of failed glucose control and the need for additional therapy beyond metformin; the rationale of the study and characteristics of the patients have been described elsewhere [18]. The loss of glucose control seen in the present study patients indicates that, because of the qualitative and quantitative decline in beta-cell function, metformin failure has already occurred at low HbA1c values and that further dose increases may have little effect. Similar assessments of data for add-on treatment with exenatide vs insulin glargine [9] have indicated that improvement in glycaemic control, particularly at lower HbA1c values, requires control of postprandial hyperglycaemia, which can be achieved with the incretin mimetic, but not with basal insulin.

In conclusion, our present findings indicate that, with increasing HbA1c, AUC increases to a greater extent for total daytime glucose than for postprandial glucose. Consequently, there is a decrease in the contribution of postprandial hyperglycaemia to total glycaemia, whereas fasting hyperglycaemia becomes more important with increasing HbA1c. This is consistent with an increasingly impaired insulin response — and particularly first-phase insulin release — at higher HbA1c levels.

Conflict of interest

G.S., B.G., B.C. and L.R. have received travel grants and remuneration as members of the EUREX study advisory board; C.K., P.K. and C.N. are employees of Eli Lilly and Company.
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