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Diabetes & Metabolism 36 (2010) 389–394

Original article

Impact of postprandial and fasting glucose concentrations on HbA_{1c} in patients with type 2 diabetes☆

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Received 22 October 2009; received in revised form 20 April 2010; accepted 21 April 2010
Available online 2 July 2010

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 (AUC_{ppg}) and total daytime concentrations > 6.1 mmol/L (AUC_{total}), 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 HbA_{1c} categories.

Results. – There was a significant linear relationship between HbA_{1c} and the derived variables of AUC_{ppg}, AUC_{total} and $\%_{ppg}$ ($P < 0.001$ for each), with explained variance greatest for AUC_{total} ($r^2 = 37.4\%$). AUC_{ppg} increased only slightly up to an HbA_{1c} of 7.0%, but showed a steeper increase in higher HbA_{1c} categories. Also, the increase in AUC_{total} with increasing HbA_{1c} was much more pronounced. As a result, the postprandial glucose excursion as a proportion of total glucose ($\%_{ppg}$) decreased across HbA_{1c} categories from 61.0% at $HbA_{1c} < 6.5\%$ to 22.0% at $HbA_{1c} \geq 9.0\%$. HOMA-IR remained virtually unchanged through all HbA_{1c} categories, while HOMA-B showed no large changes up to HbA_{1c} 7.0%, but then decreased at higher HbA_{1c} values. The $\Delta I30/\Delta G30$ ratio decreased in the HbA_{1c} 7.0–7.9% category, but did not change greatly at higher HbA_{1c} categories.

Conclusion. – With increasing HbA_{1c}, 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 HbA_{1c} levels.

Keywords: Type 2 diabetes; Postprandial hyperglycaemia; Fasting hyperglycaemia; Beta-cell function; Insulin resistance; HbA_{1c}

Résumé

Impact de la glycémie postprandiale sur le taux d'HbA_{1c} 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'HbA_{1c}.

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 (AUC_{ppg}) et des excursions glycémiques journalières totales supérieures à 6,1 mmol/l (AUC_{total}), 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'HbA_{1c} prédéfinies.

☆ EudraCT Registration Number: 2005-005448-21.

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1262-3636/$ – see front matter © 2010 Published by Elsevier Masson SAS.
doi:10.1016/j.diabet.2010.04.004

Résultats. – Il a été observé une relation linéaire significative entre l'HbA_{1c} et les variables AUC_{ppg}, AUC_{total} et %ppg ($P < 0{,}001$ respectivement), avec une variance plus importante concernant l'AUC_{totale} ($r^2 = 37{,}4\,\%$). L'AUC_{ppg} augmentait légèrement pour les HbA_{1c} inférieures ou égales à 7,0 %, et de manière plus marquée dans les classes d'HbA_{1c} plus élevées. Toutefois, l'augmentation des AUC totales étaient beaucoup plus marquées pour les valeurs élevées d'HbA_{1c}. En conséquence, la part des glycémies postprandiales dans l'hyperglycémie totale (%ppg) était plus importante dans les classes d'HbA_{1c} basses (61,0 % pour une $HbA_{1c} < 6{,}5\,\%$) et diminuait dans les classes élevées (22,0 % pour une HbA_{1c} supérieure ou égale à 9,0 %). L'HOMA-IR était comparable et abaissé dans les classes élevées d'HbA_{1c}. L'HOMA-B était comparable dans les classes d'HbA_{1c} jusqu'à 7,0 % mais diminuait pour les valeurs d'HbA_{1c} plus élevées. Le ratio $\Delta I30/\Delta G30$ était diminué dans la classe d'HbA_{1c} 7,0–7,9 % mais n'était pas très différent dans les classes d'HbA_{1c} plus élevées.

Conclusion. – Avec l'augmentation du taux d'HbA_{1c}, l'impact de l'hyperglycémie postprandiale sur l'hyperglycémie totale diminue et, à l'inverse, l'hyperglycémie à jeun joue un rôle croissant. Ces résultats sont cohérents avec une altération croissante de l'insulinosécrétion, particulièrement de la première phase de celle-ci, à des taux d'HbA_{1c} plus élevés.

Mots clés : Diabète de type 2 ; Hyperglycémie postprandiale ; Hyperglycémie à jeun ; Fonction cellules β ; Insulinorésistance ; HbA_{1c}

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 contributors to overall hyperglycaemia in patients with $HbA_{1c} < 7.3\%$, while increments in fasting glucose represent the major 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 HbA_{1c}, 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 $HbA_{1c} < 6.5\%$ to HbA_{1c} 6.5–6.9%, followed by further stepwise increments in fasting daytime and nocturnal hyperglycaemia at higher HbA_{1c} levels. The implication from these and other studies [9–11] is that control of fasting hyperglycaemia alone is not enough to achieve HbA_{1c} 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 $\geq 25\,kg/m^2$, but $\leq 40\,kg/m^2$, 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 $HbA_{1c} \geq 6.0\%$, but $\leq 10.0\%$, 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 (AUC_{ppg}) were calculated using the glucose area above the prebreakfast glucose concentration, while total hyperglycaemia (AUC_{total}) was calculated using the glucose area above 6.1 mmol/L. The percentage of hyperglycaemia due to postprandial excursions ($\%_{ppg}$) was calculated as: ($AUC_{ppg} \div AUC_{total}$) × 100%. To calculate AUC_{ppg} and AUC_{total}, 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-