Estimates of the relative and absolute diurnal contributions of fasting and post-prandial plasma glucose over a range of hyperglycaemia in type 2 diabetes

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Abstract

Aims. – To re-examine the relative and absolute contributions of fasting/pre-prandial glucose (FPG) and post-prandial glucose (PPG) to 24-h hyperglycaemia and HbA1c, respectively in non-insulin treated subjects with type 2 diabetes (T2DM).

Materials and methods. – A total of 52 T2DM subjects (37 men) had daytime 12 h plasma glucose (PG) profiles determined in response to three serial identical test meals commencing at 08:00 h with pre-prandial and frequent post-prandial blood samples collected. The overnight PG profile was derived by projecting the 2000 h glucose concentration to the pre-breakfast value at 08:00 h. PPG exposure was calculated above fasting/pre-prandial value for each meal. Excess hyperglycaemia was calculated based on a PG > 5.5 mmol/L with fasting hyperglycaemia being the difference between the two measurements. The subjects were divided into five groups according to the HbA1c (Group 1 < 7.0%; Group 2: 7.0–< 7.5; Group 3: 7.5–< 8.0%; Group 4: 8.0–< 9.0%; Group 5: ≥ 9.0%). The 24 h relative contribution of PPG exposure and fasting hyperglycaemia to excess hyperglycaemia and the absolute contribution of PPG and fasting hyperglycaemia to excess HbA1c (HbA1c – 5.1%) was calculated.

Results. – With deteriorating glycaemia, the relative contribution of PPG exposure decreased across the groups from 43.5% (HbA1c < 7.0%) to 17.8% (HbA1c ≥ 9.0%), whilst the contributions of fasting hyperglycaemia increased from 56.5% to 82.2% (P = 0.004), respectively. The absolute contributions of PPG to excess HbA1c was 0.7%, which remained relatively stable across the spectrum of HbA1c, while fasting hyperglycaemia increased significantly from groups 1 to 5 (P < 0.001).

Conclusions. – Fasting hyperglycaemia contributes substantially in all groups, increasing as HbA1c deteriorates. The absolute contribution of PPG to excess HbA1c did not vary across the range of HbA1c, representing a significant relative contribution even in well-controlled subjects with a HbA1c < 7.0%.

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Keywords: Fasting glycaemia; Post-prandial glycaemia; HbA1c; Hyperglycaemia

Résumé

Contributions diurnes, relatives et absolues, des glycémies à jeun et post-prandiales dans le diabète de type 2 en fonction du degré de l’hyperglycémie.

Buts. – Reconsidérer les contributions relatives et absolues des hyperglycémies de jeûne ou pré-prandiales (GJ) et des hyperglycémies post-prandiales (GPP) à l’hyperglycémie globale des 24 heures et leurs impacts respectifs sur l’HbA1c chez des sujets diabétiques de type 2 non traités par l’insuline (DT2).

Matériels et méthodes. – Le profil glycémique diurne de 52 sujets ayant un DT2 (37 hommes) est étudié pour déterminer la réponse glycémique à trois repas tests consécutifs, administrés toutes les quatre heures à partir de huit heures du matin, grâce à un échantillonnage sanguin fréquent réalisé en pré- et post-prandial. Les glycémies plasmatiques nocturnes sont calculées par projection de la glycémie de 20 heures sur celle de huit heures avant le petit déjeuner. À chaque repas, l’exposition post-prandiale est calculée par l’incrémentation au-dessus de la glycémie de jeûne/pré-prandiale. L’hyperglycémie de jeûne additionnelle est calculée par la différence entre la glycémie de jeûne et 5.5 mmoles/L. Les sujets sont divisés en cinq groupes en fonction de leur HbA1c (groupe 1: ≤ 7.0%; groupe 2: 7–< 7.5%; groupe 3: 7.5–< 8 %; groupe 4: 8–< 9 %; groupe 5: ≥ 9 %). Les calculs portent sur les contributions relatives de la GPP et de l’hyperglycémie de jeûne à l’hyperglycémie globale des 24 heures et l’impact absolu de la GPP et de l’hyperglycémie de jeûne sur l’excès d’HbA1c (HbA1c – 5.1 %).

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Résultats. – La contribution relative de la GPP diminue de 43.5 % (HbA1c < 7%) à 17.8 % (HbA1c ≥ 9%) quand le contrôle glycémique se détériore. En revanche, la contribution de l’hyperglycémie de jeûne augmente de 56.5 % à 82.2 % (P=0,004). L’impact absolu de la GPP sur l’HbA1c est de 0.7 % et reste relativement stable quel que soit le niveau de l’HbA1c tandis que l’impact de l’hyperglycémie de jeûne augmente significativement du groupe 1 au groupe 5 (P<0,001).

Conclusions. – La contribution des glycémies de jeûne est substantielle dans tous les groupes mais augmente avec la détérioration de l’HbA1c. L’impact absolu de la GPP sur l’HbA1c ne varie pas de manière significative entre les groupes, conduisant à une contribution relative significative, même chez les sujets ayant un bon contrôle glycémique avec une HbA1c < 7,0 %.

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Mots clés : Glycémie post-prandiale ; Glycémie à jeun ; HbA1c ; Hyperglycémie

1. Introduction

The relationship between poor overall glycemic controls as measured by HbA1c and the risk of diabetes related complications is well known. The percentage of HbA1c glycation is proportional to the life span of the erythrocyte and the ambient glucose concentration and represents a weighted average of fasting and post-prandial blood glucose levels during the preceding ~120 days, with approximate 50% contribution from the preceding month [1,2]. The seminal study by Monnier et al. in 2003 involving 290 subjects with T2DM using a four-point glucose profile over a 9 h daytime period, estimated that the relative contribution of PPG to hyperglycaemia was predominant (~70%) in reasonably well-controlled patients (HbA1c < 7.3%), decreasing to approximately 30% at HbA1c of 10% in parallel with an increasing contribution of fasting hyperglycaemia [3]. This finding led to the proposal and later confirmation that post-prandial hyperglycaemia is the initial step in the deterioration of glucose homeostasis in individuals with type 2 diabetes undergoing continuous glucose monitoring [4]. By using three standard meal tolerance tests during the day and frequent blood glucose sampling, we demonstrated that this pattern of fasting and post-prandial relative contributions to hyperglycaemia holds true and also that the absolute contributions of post-prandial glucose to HbA1c remains essentially unchanged as glycaemia deteriorates above a HbA1c of ~6.5% [5]. More recently, Riddle et al. demonstrated that in insulin treated persons with type 2 diabetes over a 24–h period, based on a seven-point PG profile (samples before and after each meal and at bedtime), fasting hyperglycaemia was the major relative contributor to total hyperglycaemia (~80%) irrespective of HbA1c at baseline [6]. The basal glucose contribution was calculated by linear extrapolation from the last blood glucose at night to the pre-breakfast value the following day. The subjects were divided into five groups according to HbA1c i.e. group 1: <8.0%, group 2: 8.0–8.5%, group 3: 8.5–9.0%, group 4: 9.0–9.5%, group 5: ≥ 9.5%. Following 24 weeks of treatment with basal insulin therapy administered at bedtime, the relative contribution of fasting hyperglycaemia to total hyperglycaemia was as expected reduced, accounting for approximately 32% to 34% for an HbA1c range of 6.5% to <8.0%. This indicates that there is still a significant residual excess PPG with a HbA1c below 8.0% in T2DM exposed to basal insulin therapy [6]. In contrast following treatment with insulin preparations comprising a prandial component, i.e. rapid acting insulin analogue, premixed insulin or even oral therapy intensification, the contribution of basal hyperglycaemia remained between 64.4% and 71.3% for the subgroups with a HbA1c below 8.0% [6].

Estimates of the relative contributions of fasting and post-prandial hyperglycaemia will be influenced by various factors especially the frequency and timing of the daytime and overnight glucose profiles and treatment regimen used. By linear extrapolation of the PG values from 20:00 h to 08:00 h projected to be the same as the fasting value of that day [7], we were able to extend our analysis to include the overnight period in our calculations to determine the relative and absolute contributions of post-prandial glucose and pre-prandial glucose to hyperglycaemia and HbA1c respectively. In addition, the use of continuous glucose monitoring, (CGM) in a smaller cohort of persons with T2DM allowed us to adjust for the slight overestimation of the fasting contribution, derived by the two-point method. We have thus re-evaluated our previous data to determine the relative and absolute contributions of PPG and fasting or pre-prandial glucose to hyperglycaemia and HbA1c respectively over a 24-h period.

2. Materials and methods

2.1. Patients and methods

Details of the methods employed have been described previously [5]. Fifty-two patients (37 men) with diagnosed T2DM on a stable dose of gliclazide, metformin or both with no significant renal, hepatic or symptomatic cardiac disease were recruited. All subjects took their oral agents during the 12-hour study days. Subjects were divided into five groups according to HbA1c (group 1: <7.0%; group 2: 7.0–<7.5%; group 3: 7.5–<8.0%; group 4: 8.0–<9.0%; Gp5: ≥ 9.0%). The local research ethics committee approved the study and all the patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Day profiles were commenced at 0800h after a 10-hour overnight fast. Fasting samples for glucose were taken at –30 min and at 0 min. Following the 0 min sample, the participants consumed a standard 500 kcal mixed meal (58% carbohydrate, 22% fat and 20% protein) within 10 min. Post-meal samples were collected every 10 min during the first hour, every 15 min during the next half hour and then half hourly over the remaining period up to 4 h after the commencement of the test meal. At 4 and 8 h from the beginning of the first meal i.e. at 12:00 h and 16:00 h, two further identical meals were consumed.
over the same period of time. The same blood sampling pattern was repeated with each meal over the total 12 h study period.

Glucose was measured by a glucose oxidase method. HbA1c measurements were DCCT aligned and determined using a high performance liquid chromatography assay (TOSOH HLC-723 G7; Tosoh Corporation, Tokyo, Japan).

2.2. Calculations

FPG was the average of the two pre-meal plasma glucose levels at -30 and 0 min. Pre-prandial plasma glucose concentrations for the second and third meals of the day were the last blood samples at 240 min following the commencement of the preceding meal. The overnight values were estimated by extrapolating linearly from the 720 min (2000 h) plasma glucose concentration to the next morning (0800 h) utilising the same fasting value as the previous day and an AUC calculated for the night time period, replicating the method of Riddle et al. [6]. We justified estimating the fasting blood glucose on the second day by using previous data from our group, where we observed a significant agreement \( P < 0.0001; r = 0.96 \) with a non-significant mean paired difference in FPG when measured on two consecutive days [7].

Different measures of hyperglycaemia were calculated from the area under the diurnal incremental plasma glucose profiles. PPG excursion for each meal was derived from the area above the pre-prandial glucose level (Fig. 1B). The total PPG excursion was the sum of the three meal time areas under the glucose profiles (PG.AUC1). Excess hyperglycaemia representing increases in both fasting and post-prandial was calculated as AUC above a plasma glucose value of 5.5 mmol/L over the 24-hour period (PG.AUC2). This plasma glucose baseline level 5.5 mmol/L was chosen as it represents the upper limit of fasting normoglycaemia as described by the ADA [8]. Fasting hyperglycaemia was then calculated as the difference between 24 h estimated excess hyperglycaemia and PPG exposure (PG.AUC2–PG.AUC1).

The relative contribution of post-prandial glucose (PG.AUC1/P.G.AUC2) × 100% and fasting hyperglycaemia [(PG.AUC2 – PG.AUC1)/PG.AUC2] × 100% to excess hyperglycaemia was then calculated for each group according to their HbA1c.

Excess HbA1c was calculated as mean HbA1c minus 5.1%, being the upper limit of normal for HbA1c with the assay used in our laboratory at the time of the study. The absolute contribution of post-prandial glucose [(mean HbA1c – 5.1%) × (PG.AUC1/P.G.AUC2)] and fasting hyperglycaemia [(mean HbA1c – 5.1%) × (PG.AUC2–PG.AUC1)/PG.AUC2] to excess HbA1c was then estimated for each group according to HbA1c.

In a separate cohort of subjects (n = 46), we calculated AUCs for the night time period (2000 to 0800) using both...
3.2. continuous glucose monitoring (Medtronic Minimed) which measured glucose at five minute intervals and the two-point AUC as described above. The separate AUCs were then compared and a significant correlation was observed ($P < 0.001$; $R^2 = 0.70$), although the two-point derived AUC overestimated the overnight contribution by $\sim 18\%$. After adjusting for this overestimation, total and fasting hyperglycaemia AUCs and contributions were also recalculated.

2.3. Statistics

Data are presented as mean $\pm$ SE. Statistical analysis was performed using SPSS for Windows version – (SPSS Inc., Chicago, IL, USA). The trapezoidal method was used to calculate all areas under the curves. Patients were divided into quintiles of HbA1c by ranking the individual HbA1c values in increasing order and using SPSS to categories them into quintiles. Differences in the respective groups were compared using non-parametric tests. A value of $P < 0.05$ was considered statistically significant.

3. Results

Demographic characteristics of patients are presented in Table 1 and the daytime glucose profiles for the five groups of HbA1c are presented in Fig. 1A.

3.1. Relative contributions

The relative contribution of post-prandial glucose and fasting hyperglycaemia to excess hyperglycaemia are represented in Fig. 2A.

The relative contribution of PPG exposure decreased across the five escalating HbA1c groups from 43.5%, 34.2%, 29.7%, 23.5% to 17.8% for groups 1 to 5 respectively, whilst the contributions of fasting hyperglycaemia increased from 56.5%, 65.8%, 70.3%, 76.5% to 82.2%, respectively. These changes in relative post-prandial and fasting percentage contributions were statistically significant ($P = 0.004$).

3.2. Absolute contributions

The absolute contribution of post-prandial glucose and fasting hyperglycaemia to excess HbA1c is represented in Fig. 2B.

The absolute contributions of post-prandial glucose to excess HbA1c in the five groups were 0.55%, 0.73%, 0.76%, 0.76%, 0.75%, respectively. There was no statistically significant difference in the absolute contribution of post-prandial glucose to HbA1c between the groups ($P = 0.601$). The absolute contribution of fasting hyperglycaemia to excess HbA1c in the five groups were 0.74%, 1.39%, 1.79%, 2.58%, 3.49%, respectively. These differences in the absolute contribution of fasting hyperglycaemia to excess HbA1c were statistically significant ($P < 0.001$).

After adjustment for overestimation of the night-time excess hyperglycaemia by the two-point method compared to CGM, the relative contributions of PPG exposure were greater whilst continuing to decrease across the five escalating HbA1c groups from 53.0%, 41.7%, 36.3%, 28.6% to 21.7% for groups 1 to 5, respectively compared to pre-adjustment values of 43.5%, 34.2%, 29.7%, 23.5% to 17.8%, respectively. The relative contributions of fasting hyperglycaemia after adjustment were 47.0%, 58.3%, 63.7%, 71.4%, 78.3% for groups 1 to 5, respectively compared to the higher, unadjusted values of 56.5%, 65.8%, 70.3%, 76.5%, 82.2%; for groups 1 to 5, respectively.

4. Discussion

There is now little doubt of the predominant role of post-prandial glucose to overall hyperglycaemia in persons with type 2 diabetes treated by diet alone or in combination with oral hypoglycaemic agents (OHA) [9]. However, controversy appears to remain in those treated with insulin preparations [6]. We have previously confirmed the findings of Monnier et al. [3] in a 12-h study looking at the relative and absolute contributions of post-prandial and fasting glucose to hyperglycaemia [5] and demonstrated that the contribution of post-prandial glucose and excess fasting glucose to overall hyperglycaemia was dependant on the level of overall glycaemia as measured by HbA1c. The relative contribution of post-prandial glucose was greatest in better-controlled subjects (HbA1c $< 7.3\%$) [5] whilst the contribution of fasting glucose became dominant as glycaemic control deteriorated. Although this pattern was maintained with all three individual meals, the actual percentages varied depending on the timing of the meal. More recently, Riddle et al. [6] examined the relative contributions of basal and post-prandial hyperglycaemia before and after insulin treatment in a large group of persons with type 2 diabetes ($n = 1699$), with a HbA1c $> 7.0\%$ from the Sanofi-Aventis development program for insulin glargine. In their population with a HbA1c ranging from $< 8.0\%$ to $\geq 9.5\%$, basal hyperglycaemia was dominant, contributing between 76% and 80% with post-prandial hyperglycaemia representing the residual 24% to 20%. However, there remained a tendency...
towards a greater contribution from post-prandial hyperglycaemia at lower ranges and from basal hyperglycaemia at higher ranges of baseline HbA1c.

In view of the continuing debate, we have re-examined our previous data to include an estimation of the overnight blood glucose profile. Our current analysis demonstrates that the original pattern of the relative contributions of fasting/basal and post-prandial excursions described by Monnier et al. [3] and ourselves [5] is maintained. However, the actual percentages of post-prandial glucose are higher compared to those of Riddle et al. in the lowest range of HbA1c (43.5% vs 24%), probably representing differences in the HbA1c range of the populations included in the two studies. Whereas in our study, we had subjects with a HbA1c < 7.0% and three further subgroups with a HbA1c < 8.0%, Riddle et al. by nature of the inclusion criteria (HbA1c > 7.0%) included subjects in the higher range. Possibly if persons with lower HbA1c had been recruited, a higher contribution by post-prandial glucose may have become apparent. It must however be pointed out that Riddle et al. had a much larger number of patients in the respective HbA1c groups.

Our present study only looked at the contributions of post-prandial and fasting hyperglycaemia at baseline in persons with T2DM on OHA treatment only. As far as we are aware, the study by Riddle et al. is the only study that has also investigated the effect of basal or prandial insulin treatment on the individual contributions where the basal insulin influenced the fasting contribution and premixed insulin treatment influenced predominantly the prandial contributions, which provides another explanation for the differences in post-prandial contribution between the two studies.
Riddle et al. [6] observed a much lower post-prandial glucose contribution (24%) compared to that calculated in the study by Monnier et al. (69.7%) [3] and our previous analysis (85.8% to 58.3% depending on the timing of the meal) [5]. This is most definitely due to the inclusion of the extrapolated overnight blood glucose profiles used as compared to daytime profiles in the two previous studies, which were based on 12-h daytime blood glucose values. This also offers an explanation for the lower values obtained by our current re-calculations (43.5%) versus our previous estimations (85.8% to 58.3% depending on the timing of the meal). As it has been pointed out by Monnier et al. [10], the seven-point self measured glycaemic profiles as used by Riddle et al. may result in under- or over-estimating the area under the blood glucose profiles. Linear extrapolation of the 720 min value to the next morning fasting level resulted in an overestimation of the night-time excess hyperglycaemia by ∼18%, when compared to continuous glucose monitoring conducted throughout the night-time period as established in a separate cohort of persons with T2DM. The overestimated excess hyperglycaemia was accounted for in our calculations by fasting hyperglycaemia only which when adjusted resulted in higher post-prandial contributions (53% to 21.7% vs 43.5% to 17.8% respectively in the five groups of HbA1c). This may offer a further explanation for the lower baseline post-prandial glucose contributions in the study of Riddle et al. CGM provides a reasonably accurate means of capturing glucose profiles and future studies employing this method in subjects with type 2 diabetes along the entire spectrum of HbA1c will prove most useful.

The absolute contributions of fasting hyperglycaemia to excess HbA1c concentration increased steeply (0.74% to 3.49%) as glycaemia deteriorated. In contrast, the absolute contributions of post-prandial glucose to excess HbA1c were not significantly different in the five HbA1c groups (0.55% to 0.76%) as previously reported [5]. Hence, the absolute impact of post-prandial glucose on excess HbA1c is ∼0.7% and is relatively stable across the glycaemic spectrum. The absolute contributions of post-prandial glucose is no different due to the renal threshold for glucose ensuring that incremental area under the glucose curves does not change appreciably with rising HbA1c.

Our recent calculations further emphasise on the remaining significant contribution of post-prandial glucose in the lower range of glycaemia (HbA1c < 7.0%). For clinicians, it will be worth noting that over a 24-h period, although fasting hyperglycaemia does contribute substantially, the contribution of post-prandial glucose is highest in patients with HbA1c < 7.0%. This has considerable clinical relevance when striving to achieve normoglycaemia, especially when basal insulin has been successfully introduced to reduce the fasting glucose but the HbA1c remains in excess of 7%. This provides the rationale for controlling the residual post-prandial glucose with prandial insulin or GLP-1 analogues and DPP-4 inhibitors.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Authors’ contributions

RP researched the data, wrote/edited the manuscript.
GD researched the data, wrote/edited the manuscript.
SDL reviewed/edited the manuscript.
DRO reviewed/edited the manuscript.

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