Relationship of glycated hemoglobin, and fasting and postprandial hyperglycemia in type 2 diabetes mellitus patients in Malaysia

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ABSTRACT
Aims/Introduction: Studies on the relative contributions of fasting and postprandial hyperglycemia (FH and PPH) to glycated hemoglobin (HbA1c) in patients with type 2 diabetes have yielded inconsistent results. We aimed to assess the relationship by using continuous glucose monitoring in a multi-ethnic cohort.

Materials and Methods: A total of 100 adults with type 2 diabetes were assessed with 6-day continuous glucose monitoring and HbA1c. Area under the curve (AUC) ≥5.6 mmol/L was defined as AUCTOTAL. AUC equal to or greater than each preprandial glucose for 4-h duration was defined as AUCPPH. The total PPH (AUCTPPH) was the sum of the various AUCPPH. The postprandial contribution to overall hyperglycemia was calculated as (AUCTPPH / AUCTOTAL) × 100%.

Results: The present study comprised of Malay, Indian, and Chinese type 2 diabetes patients at 34, 34 and 28% respectively. Overall, the mean PPH significantly decreased as HbA1c advanced (mixed model repeated measures adjusted, beta-estimate = −3.0, P = 0.009). Age (P = 0.010) and hypoglycemia (P = 0.006) predicted the contribution difference. In oral antidiabetic drug-treated patients (n = 58), FH contribution increased from 54% (HbA1c 6–6.9%) to 67% (HbA1c ≥10%). FH predominance was significant in poorly-controlled groups (P = 0.028 at HbA1c 9–9.9%; P = 0.015 at HbA1c ≥10%). Among insulin users (n = 42), FH predominated when HbA1c was ≥10% before adjustment for hypoglycemia (P = 0.047), whereas PPH was numerically greater when HbA1c was <8%.

Conclusions: FH and PPH contributions were equal in well-controlled Malaysian type 2 diabetes patients in real-world practice. FH predominated when HbA1c was ≥9 and ≥10% in oral antidiabetic drug- and insulin-treated patients, respectively. A unique observation was the greater PPH contribution when HbA1c was <8% despite the use of basal and mealtime insulin in this multi-ethnic cohort, which required further validation.

INTRODUCTION
First described more than 40 years ago1, glycated hemoglobin (HbA1c) is currently almost ubiquitous as a measure of glycemic control in diabetes mellitus2. It has been shown to correlate with the development of diabetes complications3,4, and several organizations have also endorsed its use for diagnosis5,6. HbA1c provides an indication of overall glycemic control over a 60–90-day duration7, with more recent glycemia exerting a greater influence8,9.

The relationship between fasting and postprandial glucose levels with HbA1c among patients with type 2 diabetes has been widely debated10–12, with the seminal description by Monnier et al.13 of fasting hyperglycemia (FH) predominating at higher HbA1c levels and postprandial hyperglycemia (PPH) predominating at lower HbA1c levels being the most widely
expounded. Several other studies have been carried out with contrasting results, perhaps because of differences in study populations, methodologies and antihyperglycemic therapies. In East Asians, similar findings as those of Monnier et al. with a predominance of PPH at lower HbA1c levels were reported. One of the main differences of these studies was on the HbA1c threshold in which the shift of FH and PPH predominance occurred. Wang et al. and Kikuchi et al. reported the changes in the predominance of PPH were at HbA1c <7 and <8% in Taiwanese Chinese and Japanese populations, respectively, and vice versa for FH. An interesting observation among treatment-naïve Chinese type 2 diabetes patients from Sichuan, China, was the equal contributions of FH and PPH at HbA1c 7–9%; whereas PPH predominated when HbA1c ≤7%, and FH was greater at HbA1c >9%. Of note, the shift in both FH and PPH contributions in this Chinese cohort was not as acute as previous studies, where a plateau was shown in moderate hyperglycemia patients (HbA1c 7–9%)16. Among type 1 diabetes and insulin-treated type 2 diabetes patients, a higher correlation between HbA1c and PPH was also found in a Japanese study.

In contrast, two European studies have suggested that FH had better correlation with HbA1c than PPH among type 2 diabetes patients, who were either treatment-naïve or taking oral antidiabetic drugs (OADs). Importantly, this observation was strengthened in a large insulin-treated Caucasian type 2 diabetes cohort, where FH was predominant across the HbA1c range.

The prevalence of type 2 diabetes is alarmingly high at 17.5% among adults aged ≥18 years in Malaysia, in which half of them were undiagnosed. Marked interethnic variations in the prevalence were identified; that is, Indians, Malays, Chinese, and Aborigines at 22.1, 14.6, 12.0 and 10.7% respectively. It is well recognized that Asian type 2 diabetes phenotypes have significant pancreatic β-cell dysfunction and higher insulin resistance, which can give rise to distinct daily glycemic excursions compared with Caucasian counterparts. However, there is a dearth of information on this relationship among Malaysians. Given these disparities and technological advancements that allow for more accurate glycemic assessment, we aimed to evaluate the relative contributions of FH and PPH to HbA1c, by using 6-day continuous glucose monitoring (CGM) among multi-ethnic Malaysians with type 2 diabetes in real-world settings.

**MATERIALS AND METHODS**

**Study design and participant selection**

This was a prospective observational study carried out at the University of Malaya Medical Center, an academic institution with 1,300 beds serving a population of 1.8 million in Kuala Lumpur, Malaysia. Eligible type 2 diabetes patients were consecutively enrolled from the specialized diabetes clinic into one of the following HbA1c quintiles: 6–6.9% (42–52 mmol/mol), 7–7.9% (53–63 mmol/mol), 8–8.9% (64–74 mmol/mol), 9–9.9% (75–85 mmol/mol) and ≥10% (≥86 mmol/mol). Recruitment was capped at 20 participants per quintile, giving a total of 100 participants.

The inclusion criteria were: type 2 diabetes for at least 3 months on stable doses of either OADs, insulin (basal, premix, multiple dose insulin) or OAD plus insulin combinations; HbA1c ≥6% (42 mmol/mol); estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m² (Modification of Diet in Renal Disease formula); and normal hemoglobin level. The exclusion criteria were newly diagnosed type 2 diabetes of less than 3 months; type 1 diabetes; type 2 diabetes on lifestyle intervention only; current or previous history of hospitalization in the past 3 months; presence of comorbidities (chronic liver disease, advanced cardiac disease with New York Heart Association class III/IV, malignancy and receiving steroid therapy); estimated glomerular filtration rate ≤60 mL/min/1.73 m²; conditions affecting the accuracy of HbA1c (anemia, hemoglobinopathies, blood transfusion within 3 months before and after enrolment, receiving erythropoietin therapy); and patients who were pregnant, lactating or planning for pregnancy. The research protocol was approved by the University of Malaya Medical Center Ethics Committee (MEC reference number 9885), and registered at ClinicalTrials.gov (NCT 02117154). Written informed consent was obtained from each participant before any study procedure in keeping with the Declaration of Helsinki.

Each participant underwent three 6-day CGM periods; that is, at baseline, at the end of 1 month and at the end of 2 months. All data were used in the analysis. Four-point self-monitoring blood glucose was carried out during each CGM period for calibration purposes. Blood was taken for HbA1c ≥3 months on stable doses of either OADs, insulin (basal, premix, multiple dose insulin) or OAD plus insulin combinations; HbA1c ≥6% (42 mmol/mol); estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m² (Modification of Diet in Renal Disease formula); and normal hemoglobin level. The exclusion criteria were newly diagnosed type 2 diabetes of less than 3 months; type 1 diabetes; type 2 diabetes on lifestyle intervention only; current or previous history of hospitalization in the past 3 months; presence of comorbidities (chronic liver disease, advanced cardiac disease with New York Heart Association class III/IV, malignancy and receiving steroid therapy); estimated glomerular filtration rate ≤60 mL/min/1.73 m²; conditions affecting the accuracy of HbA1c (anemia, hemoglobinopathies, blood transfusion within 3 months before and after enrolment, receiving erythropoietin therapy); and patients who were pregnant, lactating or planning for pregnancy. The research protocol was approved by the University of Malaya Medical Center Ethics Committee (MEC reference number 9885), and registered at ClinicalTrials.gov (NCT 02117154). Written informed consent was obtained from each participant before any study procedure in keeping with the Declaration of Helsinki.

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immediately before the time of each meal marked by the patient in the event log sheet was recorded as preprandial glucose. AUC above each preprandial glucose for 4 h was defined as postprandial AUC (AUC_{PPH})\(^{23}\). The total PPH (AUC_{TPPH}) was the sum of the AUC_{PPH} of every meal. The contribution of total PPH to overall glycemia was calculated as (AUC_{TPPH} / AUC_{TOTAL}) \times 100\%. The contribution of FH to overall glycemia (AUC_{FH}) was calculated as (AUC_{TOTAL} - AUC_{TPPH}) / AUC_{TOTAL} \times 100\%. Hypoglycemia was defined as the occurrence of at least two CGM readings \leq 3.3 \text{ mmol/L} within a duration of 20 min\(^{24}\).

**Statistical analysis**

SAS for Windows, version 9.3 (SAS Institute Inc., Cary, North Carolina, USA) was used for analysis. AUC was determined by using the trapezoidal rule and calculated for each day (up to 6 days for every participant), and for each CGM period (baseline, month 1 and month 2). The AUC_{TOTAL}, AUC_{FH} and AUC_{TPPH} were calculated as the average of all observed days for each CGM period separately. The average percentages of AUC_{TOTAL}, AUC_{FH} and AUC_{TPPH} obtained at three different CGM periods were subsequently calculated. P-values from the univariate analysis used to compare between quintiles of HbA\(_1c\) were generated from the \(F\)-test for continuous variables, and either the Fisher’s exact test or the Monte Carlo estimation of Fisher’s exact test for categorical variables. Longitudinal multivariate analyses were used to assess the relative contributions of FH and PPH to HbA\(_1c\), as well as to determine predictors of the relative contribution of PPH to HbA\(_1c\). In particular, mixed model repeated measures (MMRM) were fitted with average percentages of AUC_{TOTAL}, AUC_{FH} and AUC_{TPPH} obtained at three different CGM periods as the outcome, and HbA\(_1c\) as the explanatory variable. Other variables in the model included age, sex, CGM period, presence of hypoglycemia, total dose and type of insulin, and use of sulfonylurea, metformin, alpha-glucosidase inhibitor and dipeptidyl peptidase-4 inhibitors. The unstructured covariance matrix was used for all models after assessment of best fit using Bayesian information criterion. Beta-coefficients, least-squares means and least-squares mean differences with associated 95\% confidence intervals (95\% CI), and P-values were presented for continuous HbA\(_1c\) levels. Comparisons between quintiles using MMRM were adjusted for multiplicity using the Dunnet–Hsu procedure. P-values <0.05 were considered to denote statistical significance. Values quoted were mean ± standard deviation unless stated otherwise.

**RESULTS**

**Baseline clinical data**

All 100 participants completed the study, with 34\% Malays and Indians, respectively, 28\% Chinese, and 4\% other ethnicities.
The mean age and duration of type 2 diabetes were 57.0 ± 10.0 years and 13.2 ± 8.1 years, respectively. In general, the participants were obese, with a mean body mass index of 28.9 ± 5.4 kg/m² and a waist circumference of 96.8 ± 12.8 cm. The average number of recorded meals ranged from 2 to 5 meals/day. The baseline characteristics of all participants are shown in Table 1.

All participants were taking metformin, except for one who had severe metformin-related gastrointestinal intolerance. There was a significantly greater use of insulin, especially the basal-bolus regimen (P < 0.001), for participants in the higher HbA1c quintiles. Most well-controlled type 2 diabetes patients were taking OADs, whereby sulfonylureas were most commonly prescribed (P < 0.001). Use of other treatments that affect PPH (alpha-glucosidase inhibitor and incretins) were not significantly different between each quintile. The baseline medications are summarized in Table 1.

Relative contributions of FH and PPH to 24-h hyperglycemia

The relative contributions of FH and PPH to overall hyperglycemia are shown in Figure 2a. There was a statistically significant decreasing trend in mean PPH contribution to 24-h hyperglycemia with worsening control of type 2 diabetes (MMRM adjusted, Beta-estimate = −3.0, P = 0.009). In other words, the relative contribution of FH was greater as HbA1c increased. FH began to predominate when HbA1c ≥8% (64 mmol/mol). At HbA1c 8–8.9% (64–74 mmol/mol), the relative contributions

Table 1 | Patient demographic data and baseline medications

| HbA1c Quintiles | 6–6.9% (n = 20) | 7–7.9% (n = 20) | 8–8.9% (n = 20) | 9–9.9% (n = 20) | ≥10% (n = 20) | Total (n = 100) | P-value |
|-----------------|---------------|---------------|---------------|---------------|--------------|------------|--------|
| Male (%)        | 65            | 50            | 55            | 45            | 55           | 54         | 0.810 (f) |
| Age (years)     | 61.5 ± 6.3    | 58.5 ± 8.4    | 58.3 ± 10.1   | 53.6 ± 9.5    | 53.2 ± 12.9  | 57.0 ± 10.0 | 0.035 (F) |
| Race (%)        |               |               |               |               |              |            |        |
| Malays          | 40            | 35            | 25            | 20            | 50           | 34         | 0.521 (mc) |
| Indians         | 30            | 30            | 30            | 40            | 40           | 34         |        |
| Chinese         | 30            | 30            | 35            | 35            | 10           | 28         |        |
| Others†         | 0             | 5             | 10            | 5             | 0            | 4          |        |
| Duration of DM (years) | 13.2 ± 9.3 | 11.1 ± 5.4 | 13.9 ± 8.1 | 13.9 ± 8.2 | 13.9 ± 9.6 | 13.2 ± 8.1 | 0.777 (F) |
| BMI (kg/m²)     | 28.9 ± 6.4    | 29.2 ± 5.5    | 29.0 ± 4.7    | 28.7 ± 6.0    | 28.5 ± 4.6   | 28.9 ± 5.4  | 0.995 (F) |
| WC (cm)         | 95.7 ± 14.8   | 98.3 ± 15.1   | 96.6 ± 10.8   | 95.9 ± 14.2   | 97.4 ± 9.5   | 96.8 ± 12.8 | 0.967 (F) |
| Average HbA1c (%) | 6.5 ± 0.3    | 7.5 ± 0.2     | 8.4 ± 0.3     | 9.3 ± 0.4     | 11.4 ± 0.9   | 8.6 ± 1.7   | N/A    |
| SU (%)          | 60            | 75            | 60            | 30            | 15           | 48         | <0.001 (f) |
| Insulin use (%) | 15            | 20            | 30            | 60            | 85           | 42         | <0.001 (f) |
| Insulin regime (%) |            |               |               |               |              |            |        |
| Basal only      | 5             | 5             | 20            | 15            | 5            | 10         | <0.001 (mc) |
| Basal bolus     | 15            | 20            | 35            | 50            | 65           | 37         |        |
| Premix          | 0             | 5             | 5             | 5             | 20           | 9          |        |
| Prandial only   | 0             | 5             | 0             | 0             | 0            | 1          |        |
| Not on insulin  | 80            | 65            | 40            | 20            | 10           | 43         |        |
| TDD             | 67.0 ± 50.6   | 74.3 ± 61.4   | 63.5 ± 56.6   | 88.9 ± 55.2   | 87.8 ± 43.3  | 79.9 ± 51.7 | 0.667 (f) |
| AGI (%)         | 10            | 0             | 5             | 10            | 5            | 6          | 0.872 (F) |
| DPP4-I (%)      | 30            | 25            | 25            | 30            | 0            | 22         | 0.055 (f) |
| GLP-1 RAs (%)   | 0             | 5             | 10            | 0             | 0            | 3          | 0.505 (f) |

†Others (race): included Punjabis and Aborigines. AGI, alpha-glucosidase inhibitor; BMI, body mass index; DPP4-I, dipeptidyl peptidase-4 inhibitors; F, F-test; f, Fisher’s exact test; GLP-1 RAs, glucagon-like peptide-1 receptor analogs; mc, Monte Carlo estimation of Fisher’s exact test; SU, sulfonylurea; TDD, total daily dose of insulin; WC, waist circumference.
HbA1c, CGM and 24-h hyperglycemia

(a)

(b)

(c)

P = 0.037

P = 0.006

P = 0.028

P = 0.015

P = 0.047*

FH PPH

FH 51% 51% 57% 56% 61%
P PH 49% 49% 43% 44% 39%

FH 54% 54% 58% 62% 67%
P PH 46% 46% 42% 38% 33%

FH 39% 44% 54% 50% 58%
P PH 61% 50% 46% 50% 42%

FH 58% 44% 56% 50% 50%
P PH 43% 44% 44% 44% 44%

FH 49% 51% 57% 56% 61%
P PH 49% 49% 43% 44% 39%

FH 51% 51% 57% 56% 61%
P PH 49% 49% 43% 44% 39%

FH 6 – 6.9% (n = 17)
P PH 7 – 7.9% (n = 16)

FH 8 – 8.9% (n = 14)
P PH 9 – 9.9% (n = 8)

FH ≥10% (n = 3)
P PH ≥10% (n = 3)

FH 6 – 6.9% (n = 17)
P PH 7 – 7.9% (n = 16)

FH 8 – 8.9% (n = 14)
P PH 9 – 9.9% (n = 8)

FH ≥10% (n = 3)
P PH ≥10% (n = 3)

FH 6 – 6.9% (n = 3)
P PH 7 – 7.9% (n = 4)

FH 8 – 8.9% (n = 6)
P PH 9 – 9.9% (n = 12)

FH ≥10% (n = 17)
P PH ≥10% (n = 17)

FH 6 – 6.9% (n = 3)
P PH 7 – 7.9% (n = 4)

FH 8 – 8.9% (n = 6)
P PH 9 – 9.9% (n = 12)

FH ≥10% (n = 17)
P PH ≥10% (n = 17)
of FH and PPH were 57 and 43%, respectively ($P = 0.037$). FH was numerically predominant at HbA1c 9–9.9% (75–85 mmol/mol), but this did not achieve statistical significance. At HbA1c $\geq 10\%$, FH contribution was 61% as opposed to PPH contribution of 39% ($P = 0.006$). The relative contributions of FH and PPH were equal when HbA1c was $<$8% (64 mmol/mol).

The present study also examined the effect of various factors on PPH contribution to HbA1c (Table 2). Older age ($P = 0.010$) and the presence of hypoglycemia ($P = 0.006$) were the only significant predictors of greater PPH contribution to HbA1c.

Subgroup analyses

In our cohort, 58 type 2 diabetes patients were treated with OAD(s) only. The relative contribution of FH increased with deteriorating HbA1c; i.e., 54% (HbA1c 6–6.9%), 54% (7–7.9%), 58% (8–8.9%), 62% (9–9.9%) and 67% ($\geq 10\%$; Figure 2b). The significant predominance of FH was observed in poorly controlled patients with HbA1c 9–9.9% (75–85 mmol/mol; $P = 0.028$) and HbA1c $\geq 10\%$ (86 mmol/mol; $P = 0.015$). The differences in contribution between FH and PPH did not achieve statistical significance at HbA1c 6–6.9% ($P = 0.443$) and HbA1c 7–7.9% ($P = 0.486$).

There were 42 insulin-treated type 2 diabetes patients, of whom a similar trend of greater FH contribution at higher HbA1c (Figure 2c) was identified. The relative contributions of FH with HbA1c 6–6.9, 7–7.9, 8–8.9, 9–9.9, and $\geq 10\%$ were 39, 44, 54, 50 and 58%, respectively. Participants with HbA1c $\geq 10\%$ had significantly higher FH contribution ($P = 0.047$). However, this was not significant after adjusted for hypoglycemia ($P = 0.075$). On a separate note, the contribution of PPH was greater when HbA1c $<$8%, but this was not statistically significant as a result of a smaller sample size.

**DISCUSSION**

The current research was the first prospective study assessing the relative contributions of FH, PPH and HbA1c by using CGM in a multiracial type 2 diabetes cohort (Malays, Indians, Chinese) in a real-world setting. Present analysis observed that FH and PPH contributions to HbA1c were equal in relatively well-controlled type 2 diabetes patients (HbA1c $<$8%), which was consistent with previous Chinese studies. These results remained similar even with the application of the AUC calculation by Riddle et al., together with a significant predominance of FH at HbA1c 8–8.9% (57.5%, $P = 0.043$) and HbA1c $\geq 10\%$ (61.1%, $P = 0.005$) in the overall cohort. Of note, this finding was contrary to that of Monnier et al., where higher PPH contribution at lower HbA1c levels was reported among Caucasians with type 2 diabetes. A comparison between the eight studies examining this relationship is summarized in Table 3, which could have further expounded on the discrepancy of results.

The present study showed a significant trend of decreasing PPH contribution (and therefore increasing FH contribution), as HbA1c increased in both OAD- and insulin-treated multi-ethnic Malaysian type 2 diabetes patients (HbA1c $\geq$ and 10%, respectively). This added further information on the findings of previous studies, which included either drug-naïve or OAD-treated type 2 diabetes among Caucasians and East Asians only, except Kikuchi et al. who also recruited those taking basal insulin. In addition, Wang et al. reported a trend towards greater FH contribution with HbA1c $>$8% among Taiwanese Chinese, although the difference was not statistically significant. This could possibly be because their highest quintile had a very broad HbA1c range of 8.8–12.7% (73–115 mmol/mol), compared with the even HbA1c range in the present study. Overall, these data suggested that in both Caucasian and Asian patients with poorly controlled type 2 diabetes (HbA1c $\geq$8%) irrespective of treatment regimen, FH was predominant and should therefore be the focus of therapy.

Among OAD(s)-treated patients, FH and PPH contributions were equal, despite showing a non-significant trend of higher FH contribution at 54–58% with HbA1c $<$9% (75 mmol/mol) in our cohort. Previous studies, which involved mainly Caucasians and East Asians with type 2 diabetes, had mostly described the predominance of PPH at low HbA1c levels. The explanation for this variation from what had been previously observed was unclear. As the present study participants had a longer duration of type 2 diabetes, PPH contribution was hypothesized to be higher as a consequence of greater pancreatic $\beta$-cell insufficiency. However, this was not shown in the present study. The influence of OAD(s) on this relationship was taken into consideration – neither incretin therapies nor alpha-glucosidase inhibitor was found to be the significant predictor of the contribution difference. The present results were in concordance with Peter et al., where greater FH contribution remained (56.5–76.5%) when HbA1c was $<$9%.

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**Table 2** | Predictors of relative contribution of postprandial hyperglycemia to glycosylated hemoglobin

| Factors            | Estimate | $P$-value |
|--------------------|----------|-----------|
| Age                | 0.496    | 0.010     |
| Hypoglycemia       | 6.450    | 0.006     |
| Sulfonylurea        | −3.448   | 0.639     |
| Insulin            | −7.096   | 0.336     |
| Type of insulin    |          |           |
| Basal bolus        | −2.663   | 0.632     |
| Prandial only      | −18.336  | 0.552     |
| Basal only         | 8.291    | 0.428     |
| Metformin          | 4.374    | 0.795     |
| AGI                | −5.306   | 0.487     |
| DPP4-i             | −0.843   | 0.854     |

Mixed model repeated measures controlled for age, sex, continuous glucose monitoring period, presence of hypoglycemia, total dose and type of insulin, use of sulfonylurea, metformin, alpha-glucosidase inhibitor (AGI), and dipeptidyl peptidase-4 inhibitors (DPP4-i).
| Table 3 | Comparison of studies on the relationship between FH, PPH and HbA1c |
|--------|---------------------------------------------------------------|
|        | Monnier (2003) | Shimizu (2008) | Kikuchi (2010) | Riddle (2011) | Wang (2011) | Peter (2013) | Kang (2015) | Our study |
| n      | 290            | 57             | 66             | 1,699 (6 trials) | 121         | 52           | 59          | 100       |
| Type of patients | (a) Type 2 diabetes on diet control, SU or MTF | (a) Type 2 diabetes on diet control, MTF/PIO/SU or basal insulin | (b) Premix or basal bolus insulin treated | (b) Not on prandial or premix insulin & non-AGI treated | (c) Caucasian | (a) Type 2 diabetes on MTF/SU/PIO/SU or basal insulin | (b) Add on basal or premix insulin | (c) Chinese, Taiwan |
| Glucose threshold (mmol/L) | ≥6.1 (Mean HbA1c 7.83%) | ND | 5.2—18.3 | 5.6 | 5.6 | 5.6 | 5.6 |
| Methods | (a) One-day, four-point venous blood. 20/290 had 24 h CGM | (a) Six-point SMBG (1 day) | Seven-point SMBG (baseline, week 24/28) | (a) 3 day CGM (one-time period) | (a) Multiple venous blood for 4 h after each meal | (b) Three main recorded meals | (b) Three main recorded meals | (a) 6-day CGM (monthly × 3) |
| HbA1c range (%) | 6.3—11.4 | ND | 7.6—100 | 5.7—12.7 | 59—96 | Classified into ≤7, 7—9 and >9% | 60—140 |
| Key findings | Greater PPH at HbA1c <7.3% | PPH had better correlation with HbA1c | FH predominated across the HbA1c range despite on OADs | Greater PPH at HbA1c ≤7.0% | Equal FH and PPH at HbA1c >7.0% | At baseline Greater FH across the HbA1c range | After adjusted for nocturnal hypoglycemia Greater PPH at HbA1c <7.0% | Greater FH at HbA1c ≥7.0% |

AGI, alpha-glucosidase inhibitor; CGM, continuous glucose monitoring; FH, fasting hyperglycemia; HbA1c, glycated hemoglobin; MTF, metformin; ND, not documented; OADs, oral antidiabetic drugs; PIO, pioglitazone; PPH, postprandial hyperglycemia; SMBG, self-monitoring blood glucose; SU, sulfonylurea.
reporting a reduced FH contribution from 56.5 to 47.0% (and therefore greater PPH contribution) at HbA1c <7% after adjusting for overestimation of nocturnal glycemia in this British cohort, it was important to note that the reference group was a totally different population than the study participants. In drug-naive Chinese type 2 diabetes patients, equal contributions of FH and PPH at HbA1c 7–9% was shown. When HbA1c <7%, PPH contribution predominated at 77.2% in this cohort. These findings suggested that controlling FH and PPH concomitantly were important in lowering HbA1c to 7–9% in both drug-naive and OAD-treated Chinese type 2 diabetes, perhaps with greater emphasis on PPH when HbA1c <7%.

In contrast to the aforementioned findings, a non-significant trend of greater contribution of PPH at HbA1c <8% was shown among insulin-treated Malaysian type 2 diabetes patients. Furthermore, the observation of a significantly greater contribution of FH at a higher HbA1c level (≥10% in the present study) among insulin users was clinically relevant, and reinforced the importance of treating FH in poorly controlled type 2 diabetes patients.

We attempted to determine the factors that could possibly affect the contribution difference. Based on the secondary analysis, advancing age was a significant predictor of greater PPH contribution in the current Malaysian cohort. We hypothesized that this might represent a greater degree of β-cell insufficiency in older individuals. The presence of hypoglycemia did significantly predict greater PPH contribution, which might be explained by defensive eating or overcorrection of hypoglycemia leading to elevated postprandial glucose levels. As this was an observational study, these results should be interpreted with caution.

The present study had a few strengths. First, patients from three main ethnic groups, comprising of Malays, Indians, and Chinese living in Malaysia were enrolled. It is notable that the correlation of glycemic parameters can possibly be modified as sequelae of interethnic genetic and phenotypic heterogeneity. Furthermore, use of 6-day CGM provided far greater glycemic insights compared with previous studies, which mainly used self-monitoring blood glucose or discrete plasma glucose values. Just two studies used 3-day CGM. Each of our participants had a total of 18 days of CGM over a 2-month period; that is, in the 100 participants, we had a total of 1,800 days of data, which at 288 readings per day, gave a total of 518,400 glucose values. To the best of our knowledge, this represents the most comprehensive assessment in this area to date. In addition, all our participants were allowed to consume their normal routine diets, thus providing ‘real-life’ data that were reflective of daily nutritional patterns and glycemic excursions of Malaysians with type 2 diabetes. Each logged meal (not just the three main meals) was considered in the analysis, which again contributed to the robustness of our data. Of note, our cohort had the widest HbA1c range compared with other studies; that is, 6–14% (42–130 mmol/mol).

A few limitations were recognized in the present study. First, the detectable glucose range of CGM was between 2.2–22.2 mmol/L, and a small number of participants had readings above or below these values. Second, we relied on our participants to have accurate logs of their mealtimes to facilitate PPH measurements as precise as possible. Third, we were not able to capture the glycemic profiles on non-CGM days, which would have provided further robustness to our data. Better dietary and drug adherence on CGM days could be observed, especially when participants were aware that they were under monitoring (Hawthorne effects). Fourth, the repetitive CGM carried out at different intervals on the same individuals could contribute to the possible bias on the assessment of FH and PPH contributions. Nevertheless, applying the MMRM analysis took into account this possibility, together with better between-subject correlations at different time-intervals, could help in minimizing the potential bias. It would be good to have the subgroup analysis on single ethnicity-based contribution differences. However, the present sample size was limited to detect such variations.

In conclusion, the present study, by utilizing 6-day CGM, observed equal contributions of FH and PPH among multi-ethnic Malaysians with well-controlled type 2 diabetes (HbA1c <8%) in real-world practice. The contribution of PPH declined progressively when HbA1c advanced in both OAD- and insulin-treated type 2 diabetes patients. In a real-life setting, FH was the main contributor when HbA1c was ≥9% in OAD-treated patients and ≥10% among insulin users. A unique observation that required further validation was the greater contribution of PPH when HbA1c <8%, despite the use of both basal and mealtime insulin. CGM was an accurate glycemic monitoring tool in daily clinical practice, as reflected in the present study. Future research on this relationship by ethnicity, focusing on Asian patients, is important in view of the genetic and phenotypic disparities in the type 2 diabetes population. Our observations also call for more studies with larger sample sizes to verify the effects of insulin therapy on FH and PPH contributions across HbA1c ranges. These findings are crucial, as they provide a useful guide to clinicians in personalizing the treatment regimens for Asians with type 2 diabetes.

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DISCLOSURE
The authors declare no conflict of interest.
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