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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 (HbA_{1c}) 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 HbA_{1c}. Area under the curve (AUC) ≥5.6 mmol/L was defined as AUC_{TOTAL}. AUC equal to or greater than each preprandial glucose for 4-h duration was defined as AUC_{PPH}. The total PPH (AUC_{TPPH}) was the sum of the various AUC_{PPH}. The postprandial contribution to overall hyperglycemia was calculated as (AUC_{TPPH} / AUC_{TOTAL}) × 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 HbA_{1c} 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% (HbA_{1c} 6–6.9%) to 67% (HbA_{1c} ≥10%). FH predominance was significant in poorly-controlled groups ($P = 0.028$ at HbA_{1c} 9–9.9%; $P = 0.015$ at HbA_{1c} ≥10%). Among insulin users ($n = 42$), FH predominated when HbA_{1c} was ≥10% before adjustment for hypoglycemia ($P = 0.047$), whereas PPH was numerically greater when HbA_{1c} was <8%.

Conclusions: FH and PPH contributions were equal in well-controlled Malaysian type 2 diabetes patients in real-world practice. FH predominated when HbA_{1c} was ≥9 and ≥10% in oral antidiabetic drug- and insulin-treated patients, respectively. A unique observation was the greater PPH contribution when HbA_{1c} 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 ago[1], glycated hemoglobin (HbA_{1c}) is currently almost ubiquitous as a measure of glycemic control in diabetes mellitus[2]. It has been shown to correlate with the development of diabetes complications[3,4], and several organizations have also endorsed its use for diagnosis[5,6]. HbA_{1c} provides an indication of overall glycemic control over a 60–90-day duration[7], with more recent glycemia exerting a greater influence[8,9].

The relationship between fasting and postprandial glucose levels with HbA_{1c} among patients with type 2 diabetes has been widely debated[10–12], with the seminal description by Monnier *et al.*[13] of fasting hyperglycemia (FH) predominating at higher HbA_{1c} levels and postprandial hyperglycemia (PPH) predominating at lower HbA_{1c} levels being the most widely

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expounded. Several other studies have been carried out with contrasting results, perhaps because of differences in study populations, methodologies and antihyperglycemic therapies[14–20].

In East Asians, similar findings as those of Monnier *et al.* with a predominance of PPH at lower HbA_{1c} levels were reported[14–16]. One of the main differences of these studies was on the HbA_{1c} threshold in which the shift of FH and PPH predominance occurred[14–16]. Wang *et al.*[14] and Kikuchi *et al.*[15] reported the changes in the predominance of PPH were at HbA_{1c} <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 HbA_{1c} 7–9%; whereas PPH predominated when HbA_{1c} ≤7%, and FH was greater at HbA_{1c} >9%[16]. 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 (HbA_{1c} 7–9%)[16]. Among type 1 diabetes and insulin-treated type 2 diabetes patients, a higher degree of correlation between HbA_{1c} and PPH was also found in a Japanese study[17].

In contrast, two European studies have suggested that FH had better correlation with HbA_{1c} than PPH among type 2 diabetes patients, who were either treatment-naïve or taking oral antidiabetic drugs (OADs)[18,19]. Importantly, this observation was strengthened in a large insulin-treated Caucasian type 2 diabetes cohort, where FH was predominant across the HbA_{1c} range[20].

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[21]. 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[21]. 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[22]. 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 HbA_{1c} by using 6-day continuous glucose monitoring (CGM) among multiethnic 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 medical 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 HbA_{1c} 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; HbA_{1c} ≥6% (42 mmol/mol); estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 (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 m^2; conditions affecting the accuracy of HbA_{1c} (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 988.5), 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 HbA_{1c} level at baseline, month 1 and month 2. Every participant completed an event log sheet during each CGM period. All meals recorded by participants were included in the analysis. Management of type 2 diabetes of enrolled patients was based on the investigators' discretion, as per standard of care throughout the study period.

CGM

CGM was carried out using iPro™2 with Enlite sensors (Medtronic International, Northridge, California, USA), with 288 readings per day for 6 days. As CGM was not real-time, glucose readings were downloaded for analysis at the end of each 6-day period. Each participant carried out self-monitoring blood glucose using Roche Accuchek Performa glucometers (glucose range of 0.6–33.3 mmol/L and hematocrit range of 10–65%). HbA_{1c} was analyzed by using the ion-exchange high-performance liquid chromatography method (NGSP/DCCT-aligned; Bio-Rad Variant™ II Turbo; Bio-Rad, Hercules, California, USA). Its correlations of variance (CV) were <2% (intra-assay) and <2.3% (interassay).

Our definitions of glycemic area under the curve (AUC) were similar to previous studies[13,14,19,23] (Figure 1). The lowest glucose threshold was set at 5.6 mmol/L[13,14,19,23]. AUC ≥5.6 mmol/L was defined as AUC_{TOTAL}. The glucose value

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}) × 100%. The contribution of FH to overall glycemia (AUC_{FH}) was calculated as (AUC_{TOTAL} − AUC_{TPPH})/ AUC_{TOTAL} × 100%. Hypoglycemia was defined as the occurrence of at least two CGM readings ≤3.3 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

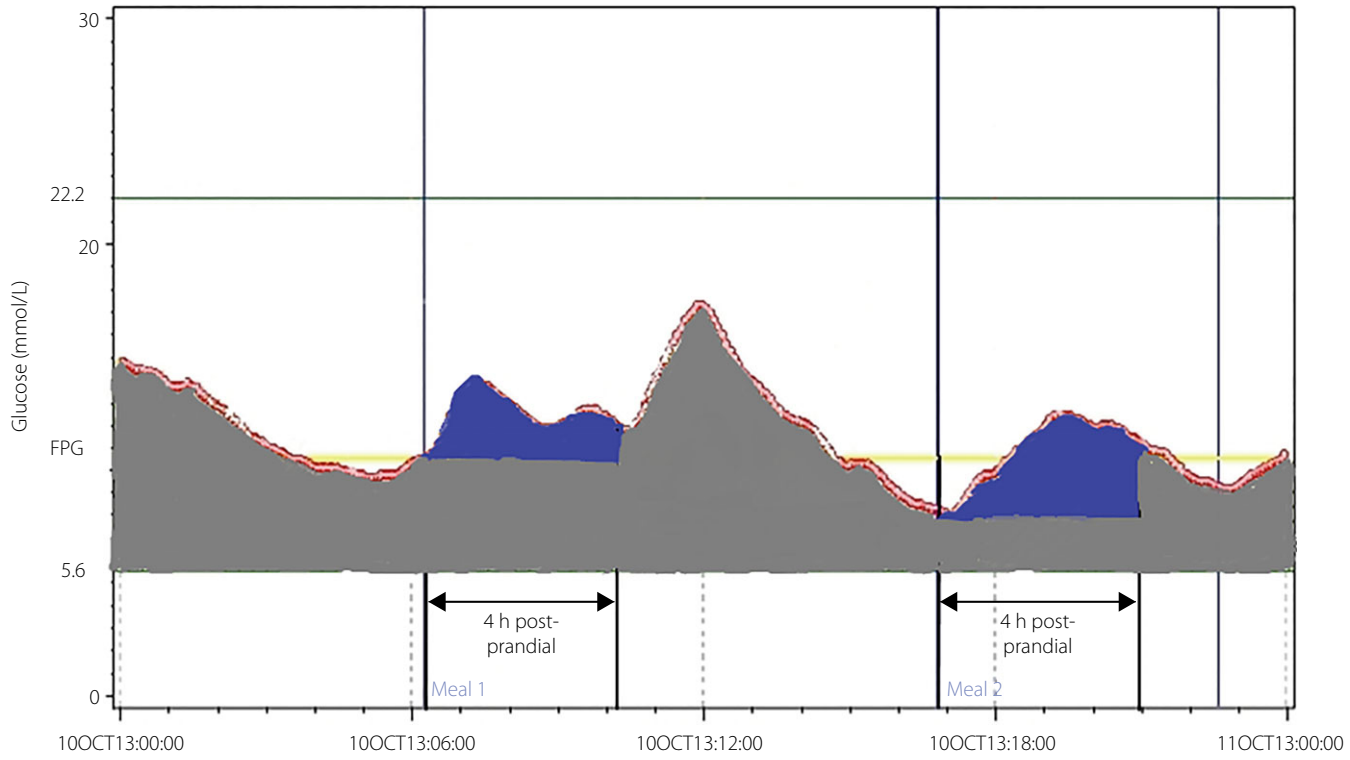


Figure 1 | Definitions of glycemic area under the curve (AUC). AUC_{TOTAL}, AUC ≥5.6 mmol/L; AUC_{PPH}, AUC above each preprandial glucose (blue shaded areas); AUC_{FH}, AUC_{TOTAL} − AUC_{PPH} (grey shaded areas).

Table 1 | Patient demographic data and baseline medications

HbA_{1c} 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/m^2)	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 HbA_{1c} (%)	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	15	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.

(Punjabis, Aborigines). 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/m^2 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.

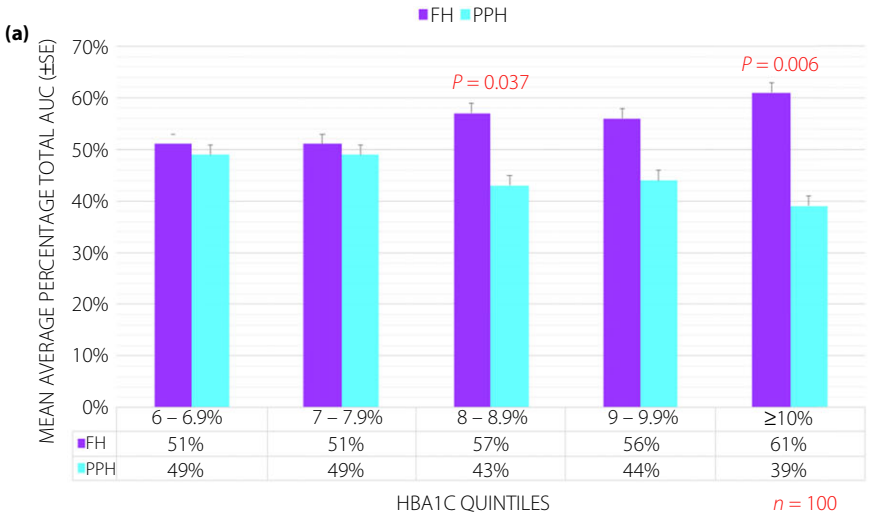
All participants were taking metformin, except for one who had severe metformin-related gastrointestinal intolerance. There was a significantly greater use of insulin, especially the basal–bolus regimen ($P < 0.001$), for partcipants in the higher HbA_{1c} quintiles. Most well-controlled type 2 diabetes 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.

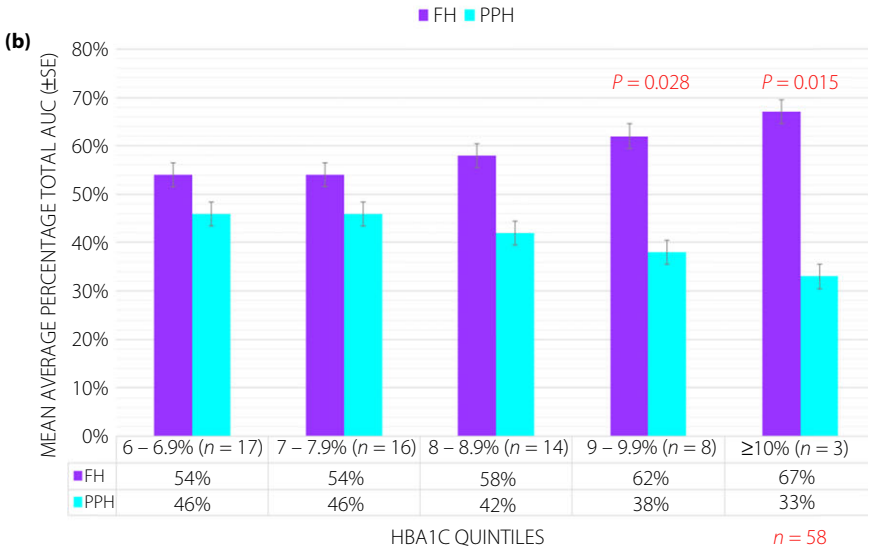
Relative contributions of FH and PPH to 24-h hyperglycemia

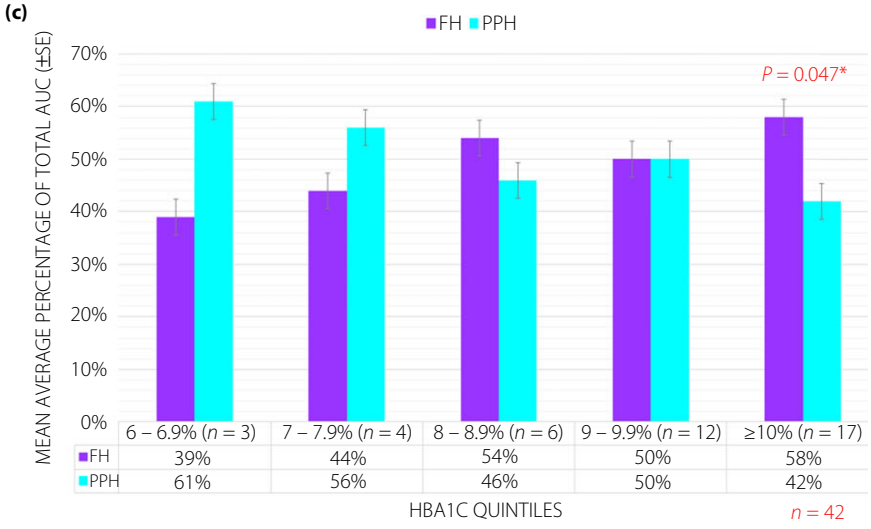
The relative contributions of FH and PPH to overall hyperglycemia are shown in Figure 2a. There was a statistically significant decreasing trend in mean PPH contribution to 24-h hyperglycemia with worsening control of type 2 diabetes (MMRM adjusted, Beta-estimate = –3.0, $P = 0.009$). In other words, the relative contribution of FH was greater as HbA_{1c} increased.

FH began to predominate when HbA_{1c} ≥8% (64 mmol/mol). At HbA_{1c} 8–8.9% (64–74 mmol/mol), the relative contributions

Figure 2 | Relative contribution of fasting hyperglycemia (FH) and postprandial hyperglycemia (PPH) to glycated hemoglobin (HbA_{1c}) by mixed model repeated measures analysis. (a) Overall cohort (n = 100). There was a significantly decreasing trend in mean PPH as HbA_{1c} increased (mixed model repeated measures adjusted, Beta-estimate = –3.0, $P = 0.009$). (b) Oral antidiabetic agents-treated type 2 diabetes patients (n = 58). (c) Insulin-treated type 2 diabetes patients (n = 42). A greater contribution of FH was observed before the adjustment for hypoglycemia at HbA_{1c} ≥10% ($P = 0.047$)*. However, the contribution difference was not significant after adjusted for hypoglycemia ($P = 0.075$). 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, and dipeptidyl peptidase-4 inhibitors. AUC, area under the curve; SE, standard error.







of FH and PPH were 57 and 43%, respectively ($P = 0.037$). FH was numerically predominant at HbA_{1c} 9–9.9% (75–85 mmol/mol), but this did not achieve statistical significance. At HbA_{1c} ≥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 HbA_{1c} was <8% (64 mmol/mol).

The present study also examined the effect of various factors on PPH contribution to HbA_{1c} (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 HbA_{1c}.

Subgroup analyses

In our cohort, 58 type 2 diabetes patients were treated with OAD(s) only. The relative contribution of FH increased with deteriorating HbA_{1c}; i.e, 54% (HbA_{1c} 6–6.9%), 54% (7–7.9%), 58% (8–8.9%), 62% (9–9.9%) and 67% (≥10%; Figure 2b). The significant predominance of FH was observed in poorly controlled patients with HbA_{1c} 9–9.9% (75–85 mmol/mol; $P = 0.028$) and HbA_{1c} ≥10% (≥86 mmol/mol; $P = 0.015$). The differences in contribution between FH and PPH did not achieve statistical significance at HbA_{1c} 6–6.9% ($P = 0.443$) and HbA_{1c} 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 HbA_{1c} (Figure 2c) was identified. The relative contributions of FH with HbA_{1c} 6–6.9, 7–7.9, 8–8.9, 9–9.9, and ≥10% were 39, 44, 54, 50 and 58%, respectively. Participants with HbA_{1c} ≥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 HbA_{1c} <8%, but this was not statistically significant as a result of a smaller sample size.

Table 2 | Predictors of relative contribution of postprandial hyperglycemia to glycated 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).

DISCUSSION

The current research was the first prospective study assessing the relative contributions of FH, PPH and HbA_{1c} 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 HbA_{1c} were equal in relatively well-controlled type 2 diabetes patients (HbA_{1c} <8%), which was consistent with previous Chinese studies[14,16]. These results remained similar even with the application of the AUC calculation by Riddle *et al.*[20], together with a significant predominance of FH at HbA_{1c} 8–8.9% (57.5%, $P = 0.043$) and HbA_{1c} ≥10% (61.1%, $P = 0.005$) in the overall cohort. Of note, this finding was contrary to that of Monnier *et al.*[13], where higher PPH contribution at lower HbA_{1c} 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 HbA_{1c} increased in both OAD- and insulin-treated multiethnic Malaysian type 2 diabetes patients (HbA_{1c} ≥9 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.*[15] who also recruited those taking basal insulin[13,16,19]. In addition, Wang *et al.*[14] reported a trend towards greater FH contribution with HbA_{1c} >8% among Taiwanese Chinese, although the difference was not statistically significant. This could possibly be because their highest quintile had a very broad HbA_{1c} range of 8.8–12.7% (73–115 mmol/mol), compared with the even HbA_{1c} range in the present study. Overall, these data suggested that in both Caucasian and Asian patients with poorly controlled type 2 diabetes (HbA_{1c} ≥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 HbA_{1c} <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 HbA_{1c} levels[13–16]. 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 β-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.*[19], where greater FH contribution remained (56.5–76.5%) when HbA_{1c} was <9%. Despite

Table 3 | Comparison of studies on the relationship between FH, PPH and HbA_{1c}

	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 (b) Non-insulin & non-AGI treated (c) Caucasians	(a) 15 Type 1 diabetes, 42 Type 2 diabetes (b) Premix or basal bolus Insulin treated (c) Japanese	(a) Type 2 diabetes on diet control, MTF/PIO/SU or basal insulin (b) Not on prandial or premix insulin & non-AGI treated (c) Japanese	(a) Type 2 diabetes on MTF/SU or both (b) Add on basal or premix insulin (c) 94.6% White	(a) Type 2 diabetes on MTF & SU/AGI (b) Non-insulin treated (c) Chinese, Taiwan	(a) Type 2 diabetes on SU/MTF, or both (b) Non-insulin treated (c) Caucasians	(a) Newly diagnosed Type 2 diabetes (b) Drug-naïve (c) Chinese, China	(a) Type 2 diabetes on all treatment regimes (b) 58%: insulin use (c) Multi-ethnic (Malays, Indians, Chinese)
Glucose threshold (mmol/L)	≥6.1	ND (Mean HbA_{1c} 7.83%)	5.2–18.3	≥5.6	≥5.6	≥5.6	≥6.1	≥5.6
Methods	(a) One-day, four-point venous blood. 20/290 had 24 h CGM (b) Two standardized meals	Six-point SMBG (1 week)	(a) Six-point SMBG (1 day) (b) Three standardized meals	Seven-point SMBG (baseline, week 24/28)	(a) 3-day CGM (one-time period) (b) Three main recorded meals	(a) Multiple venous blood for 4 h after each meal (b) Three standardized meals	3-day CGM (one-time period)	(a) 6-day CGM (monthly ×3) (b) All recorded meals
HbA_{1c} range (%)	6.3–11.4	ND	5.7–12.5	7.6–10.0	5.7–12.7	5.9–9.6	Classified into ≤7, 7–9 and >9%	6.0–14.0
Key findings	Greater PPH at HbA_{1c} <7.3% Greater FH at HbA_{1c} ≥9.3%	PPH had better correlation with HbA_{1c}	PPH strongly correlated at HbA_{1c} <8.0%, and vice versa for FH	FH predominated across the HbA_{1c} range despite on OAD(s)	Greater PPH at HbA_{1c} ≤7.0% Equal FH and PPH at HbA_{1c} >7.0%	At baseline: Greater FH across the HbA_{1c} range After adjusted for nocturnal hypoglycemia: Greater PPH at HbA_{1c} <7.0% Greater FH at HbA_{1c} ≥7.0%	Greater PPH at HbA_{1c} ≤7.0% Equal FH and PPH at HbA_{1c} 7.0–9.0% Greater FH at HbA_{1c} >9.0%	Equal FH and PPH at HbA_{1c} <8.0% Greater FH at HbA_{1c} ≥8.0%

AGI, alpha-glucosidase inhibitor; CGM, continuous glucose monitoring; FH, fasting hyperglycemia; HbA_{1c}, 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 HbA_{1c} <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[19]. In drug-naïve Chinese type 2 diabetes patients, equal contributions of FH and PPH at HbA_{1c} 7–9% was shown[15]. When HbA1c <7%, PPH contribution predominated at 77.2% in this cohort[15]. These findings suggested that controlling FH and PPH concomitantly were important in lowering HbA_{1c} to 7–9% in both drug-naïve and OAD-treated Chinese type 2 diabetes, perhaps with greater emphasis on PPH when HbA_{1c} <7%.

In contrast to the aforementioned findings, a non-significant trend of greater contribution of PPH at HbA_{1c} <8% was shown among insulin-treated Malaysian type 2 diabetes patients. Furthermore, the observation of a significantly greater contribution of FH at a higher HbA_{1c} 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[14,16]. 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 HbA_{1c} 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 multiethnic Malaysians with well-controlled type 2 diabetes (HbA_{1c} <8%) in real-world practice. The contribution of PPH declined progressively when HbA_{1c} advanced in both OAD- and insulin-treated type 2 diabetes patients. In a real-life setting, FH was the main contributor when HbA_{1c} 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 HbA_{1c} <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 HbA_{1c} 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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