Received: 18 December 2020 | Accepted: 2 March 2021

DOI: 10.1111/dom.14370

ORIGINAL ARTICLE

WILEY

Fasting and postprandial plasma glucose contribution to glycated haemoglobin and time in range in people with type 2 diabetes on basal and bolus insulin therapy: Results from a pooled analysis of insulin lispro clinical trials

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Funding information
This study and the studies included in the pooled analysis were funded by Eli Lilly and Company

Abstract

Aims: To investigate the interrelations between glycaemic metrics of fasting plasma glucose (FPG), postprandial glucose (PPG), glycated haemoglobin (HbA1c), and percentage of time in target range 3.9 to 10.0 mmol/L (%TIR) in patients on insulin therapy.

Materials and methods: A pooled analysis was conducted using datasets extracted from an integrated database of insulin lispro clinical trials (Eli Lilly and Company). Studies in patients with type 2 diabetes on basal-bolus or basal-plus insulin therapy, and with ≥7-point self-monitored blood glucose profiles were included in the analysis. A multivariate regression model was used to quantify the contribution of FPG and PPG change to the change in HbA1c and %TIR. In addition, a linear regression model was used to describe the relationship between %TIR and HbA1c.

Results: Five studies encompassing 1572 patients met the criteria for inclusion. On average, a 1-mmol/L change in FPG was associated with 2.7 mmol/mol (0.25%) change in HbA1c (range 2.0 to 2.8 mmol/mol [0.18%–0.26%]; all P <0.0001), and a 1-mmol/L change in PPG with 1.8 mmol/mol (0.16%) change in HbA1c (range 1.2 to 2.1 mmol/mol [0.11%–0.19%]; all P <0.01). Furthermore, a 1-mmol/L reduction in FPG and PPG was associated with an increase in TIR of 6.5% (range 5.8%–9.2%) and 5.3% (range 4.1%–8.7%), respectively, all P <0.0001. A decrease in HbA1c of 10.9 mmol/mol (1%) corresponded with an increase in TIR of 8.3%, on average.

Conclusions: In patients with type 2 diabetes on basal-bolus or basal-plus insulin therapy, management of both FPG and PPG is important for achievement of HbA1c and TIR goals.

KEYWORDS
database research, glycaemic control, insulin therapy, type 2 diabetes

1 | INTRODUCTION

Diabetes management is focused on controlling acute glycaemic variations in order to achieve long-term glycaemic goals. Glycated haemoglobin (HbA1c) provides an average of an individual's long-term glucose exposure and is the "gold standard" test for long-term glycaemic control. In order to achieve HbA1c goals, it is essential to manage fasting plasma glucose (FPG) and postprandial glucose (PPG): an interrelationship described as the glucose triad.[1] Elevated FPG and PPG have been shown to contribute to elevated HbA1c at different degrees during disease progression[2,3]; however, little is known about the effectiveness of treatments that aim to manage FPG and PPG, particularly among those who require basal and bolus insulin treatment. Understanding the impact of FPG and PPG improvement on HbA1c in patients receiving insulin treatment is necessary, especially with the advent of more innovative insulins that further improve FPG and PPG.

A rise in the use of continuous glucose monitoring (CGM) technology in recent years offers opportunities for more precise daily FPG and PPG management using CGM-derived metrics. One of these metrics, time in target range (TIR), defined as the time spent in the range between 3.9 and 10 mmol/L (70–180 mg/dL), has been associated with risk of diabetes-related complications and HbA1c.[4,5] As the use of metrics beyond HbA1c becomes more common practice, it is important to recognize how they are related and can best be leveraged in the management of diabetes.

The purpose of this pooled analysis was to use datasets from an integrated database of insulin lispro clinical trials from Eli Lilly and Company to investigate the contributions of FPG and PPG management in lowering HbA1c in people with type 2 diabetes on a basal-bolus or basal-plus insulin regimen. Furthermore, the study investigated the relationship between FPG/PPG and TIR and between TIR and HbA1c in this demographic.

2 | METHODS

2.1 | Search strategy and eligibility criteria

Relevant studies were identified through a systematic search of an integrated database of insulin lispro (Humalog®) clinical trials conducted by Eli Lilly and Company. This privately owned database includes 53 insulin lispro clinical trials conducted between 1992 and 2014. We included randomized controlled trials that investigated the efficacy of insulin lispro in patients with type 2 diabetes. Inclusion criteria were as follows: the study treatment had to include basal and bolus insulin therapy; the specified treatment duration had to be between 24 and 26 weeks; and participants must have collected ≥7 self-monitored blood glucose (SMBG) profiles that covered premeal and 2 hours post-meal for the three main meals (morning, midday and evening), and bedtime or 3:00 AM.

A total of five studies conducted between 2004 and 2013 contained at least one treatment arm that met the above inclusion criteria, as shown in Table 1. Only the treatment arms meeting the study inclusion criteria were included in the analysis. All five studies were open-label, parallel-treatment studies in patients with type 2 diabetes. Further information on the population characteristics and number of participants in this pooled analysis are presented in Table 2. All trials were conducted in accordance with the principles of the Declaration of Helsinki (2000), International Conference on Harmonization, and the E6 Guideline for Good Clinical Practice. Institutional review board approval and written informed consent from all the participants were obtained before conducting any evaluations or study procedures. The trials were registered at ClinicalTrials.gov.

2.2 | Analysis population

The analysis population was defined as randomized patients who received study treatment and had nonmissing HbA1c and SMBG measurements at baseline and at the end of the treatment period (24 or 26 weeks). Nonmissing SMBG was defined as having nonmissing SMBG values at ≥4 time points which included morning premeal and at least three time points among morning postmeal, midday premeal and postmeal, evening premeal and postmeal, and bedtime or 3:00 AM.

2.3 | Statistical analyses

In this pooled analysis, FPG was defined as the morning premeal SMBG value. PPG daily mean was the average of the morning, midday and evening postmeal SMBG values. Non-FPG daily mean was the average of all the SMBG values excluding FPG value.

The %TIR was derived from the seven- or eight-point SMBG profiles from individuals enrolled in the respective studies, a method similar to that employed in a post hoc analysis of the Diabetes Control and Complications Trial (DCCT) evaluating the association of TIR with the risk of microvascular complications.[6] Only valid SMBG profiles were used to calculate %TIR at baseline and endpoint. At least five SMBG values per day were required in order for an SMBG profile to be considered valid and to be included in the calculation of TIR. To estimate the %TIR for each valid SMBG profile, the number of SMBG values within the target range 3.9 to 10.0 mmol/L was divided by the number of nonmissing SMBG values for that valid profile and multiplied by 100. The %TIR at baseline and endpoint for the individual was then calculated as the average of the %TIR from valid SMBG days at baseline and endpoint, respectively.

All data were analysed using SAS version 9.4. Individual study results were presented, as well as pooled analyses across the five studies. For continuous measurements, summary statistics included sample size, mean and standard deviation (SD). Summary statistics for continuous measures were provided for baseline and the change from baseline measurements.

Regression models were used to quantify the contribution of changes in FPG and PPG to changes in HbA1c and %TIR, and to analyse the relationship between %TIR and HbA1c. For these linear

TABLE 1 Lispro integrated database type 2 diabetes studies meeting inclusion criteria

	Treatment arms	SMBG profile	Includes 3:00 AM or bedtime	SMBG week[a]	Prandial naïve	Target blood glucose values	HbA1c entry criteria, mmol/mol (%)
NCT00110370	Glargine once daily + lispro three times daily	8-point	Both	24	Yes	Fasting and premeal <6.1 mmol/L (110 mg/dL); 2-hour postmeal <7.8 mmol/L (140 mg/dL)	58.5-107.7 (7.5–12)
NCT00377858	Glargine once daily ± lispro once/twice/three times daily	7-point	3:00 AM	24	Yes	Fasting and premeal 4.4–5.6 mmol/L (80–100 mg/dL); bedtime 4.4–6.1 mmol/L (80–110 mg/dL)	58.5-107.7 (7.5–12)
NCT01215955	Glargine once daily + lispro once/twice/three times daily	7-point	3:00 AM	24	Yes	Fasting and premeal 4.7–6.4 mmol/L (85–115 mg/dL)	53.0-107.7 (7–12)
NCT01175811	Glargine once daily + lispro three times daily	7-point	3:00 AM	24	No	Fasting and premeal <6.1 mmol/L (110 mg/dL); 2-hour postmeal <7.8 mmol/L (140 mg/dL)	53.0-107.7 (7–12)
NCT01175824	Glargine once daily + lispro once daily	7-point	Bedtime	24	Yes	Fasting and premeal <6.1 mmol/L (110 mg/dL)	58.5-91.3 (7.5–10.5)

Abbreviation: SMBG, self-monitored blood glucose.

[a]SMBG week only lists the week 24 or week 26 visit, with week number counted from randomization.

regression models, coefficient estimates, standard errors of the coefficient estimates, and associated *P* values were provided. The coefficient estimates measured the degree of association between the independent and dependent variables.

2.3.1 | FPG/PPG to HbA1c

It was hypothesized that the change in HbA1c was dependent on the sum of the change in the morning premeal SMBG value (FPG) and the change in the average of SMBG values minus the FPG. A multivariate regression model was used as the primary analysis model to quantify the contribution of FPG and PPG change to the change in HbA1c. The primary regression analysis model for the change from baseline in HbA1c included intercept, change from baseline in FPG and change from baseline in (PPG daily mean – FPG) as covariates. A sensitivity analysis was also performed to confirm findings from the primary model where PPG was instead defined as the average of all SMBG values excluding FPG (non-FPG SMBG daily mean) minus the FPG. The sensitivity regression analysis model for the change from baseline in HbA1c included intercept, change from baseline in FPG and change from baseline in (non-FPG SMBG daily mean – FPG) as covariates.

2.3.2 | FPG/PPG to %TIR

The primary and sensitivity models for investigating the relationship between FPG/PPG and %TIR were similar to those for FPG/PPG to HbA1c. The primary regression analysis model for the change from baseline in %TIR included intercept, change from baseline in FPG and change from baseline in (PPG daily mean – FPG) as covariates. The sensitivity regression analysis model for the change from baseline in %TIR included intercept, change from baseline in FPG and change from baseline in (non-FPG SMBG daily mean – FPG) as covariates.

2.3.3 | %TIR to HbA1c

A linear regression model was used to analyse the relationship between the change in %TIR and change in HbA1c at endpoint. The regression analysis model for the change from baseline in %TIR included intercept and change from baseline in HbA1c as a covariate.

3 | RESULTS

3.1 | Individual trial characteristics

A total of five randomized clinical trials met the criteria for inclusion in the pooled analysis: NCT00110370 (Comparing Pre-Mixed Insulin With Insulin Glargine Combined With Rapid-Acting Insulin in Patients With Type 2 Diabetes),[7] NCT00377858 (Comparison of Two Approaches to Insulin Therapy in Patients With Type 2 Diabetes),[8] NCT01215955 (Study of Insulin Lispro in Participants With Inadequately Controlled Type 2 Diabetes [AUTONOMY]),[9] NCT01175811 (A Study Comparing Insulin Intensification Therapies in Patients With

TABLE 2 Key study characteristics

	NCT00110370 N = 130	NCT00377858 N = 203	NCT01215955 N = 838	NCT01175811 N = 185	NCT01175824 N = 216	Overall N = 1572
Age, years	54.2 (9.3)	59.5 (10.0)	57.9 (9.5)	57.8 (9.2)	57.3 (8.9)	57.7 (9.5)
Sex, n (%)						
Male	73 (56.2)	103 (50.7)	380 (45.3)	101 (54.6)	88 (40.7)	745 (47.4)
Female	57 (43.8)	100 (49.3)	458 (54.7)	84 (45.4)	128 (59.3)	827 (52.6)
Duration of diabetes, years	11.9 (6.1)	12.0 (7.4)	12.1 (6.7)	15.3 (6.7)	10.4 (6.6)	12.2 (6.8)
BMI, kg/m^2	35.1 (5.5)	28.9 (4.5)	33.1 (5.3)	25.8 (3.3)	29.8 (5.2)	31.4 (5.7)
HbA1c, mmol/mol						
Baseline	73.4 (11.8)	78.9 (12.6)	67.4 (10.2)	70.8 (11.5)	70.5 (8.2)	70.3 (11.3)
Endpoint	49.8 (7.9)	54.9 (8.5)	55.6 (11.8)	58.6 (11.0)	59.3 (11.0)	55.8 (11.3)
HbA1c, %						
Baseline	8.87 (1.08)	9.37 (1.15)	8.32 (0.93)	8.63 (1.05)	8.60 (0.75)	8.58 (1.03)
Endpoint	6.71 (0.72)	7.17 (0.78)	7.24 (1.08)	7.51 (1.01)	7.58 (1.01)	7.26 (1.03)
% Time in range 3.9–10.0 mmol/L						
Baseline	30.3 (21.8)	37.2 (28.3)	48.3 (26.3)	48.0 (23.2)	61.7 (22.5)	47.2 (26.6)
Endpoint	70.1 (20.6)	79.5 (17.5)	82.2 (18.7)	74.3 (20.6)	80.3 (20.1)	79.6 (19.5)
FPG, mmol/L						
Baseline	9.8 (3.12)	10.1 (2.69)	6.6 (1.76)	8.8 (2.15)	6.4 (1.47)	7.5 (2.53)
Endpoint	8.1 (2.35)	6.3 (1.68)	6.7 (1.66)	7.4 (1.40)	6.2 (1.21)	6.8 (1.73)
PPG, mmol/L						
Baseline	14.5 (3.62)	13.3 (3.05)	10.8 (2.41)	12.0 (2.66)	10.6 (2.05)	11.5 (2.88)
Endpoint	8.6 (2.20)	8.7 (1.90)	8.1 (1.87)	9.3 (1.79)	8.8 (1.86)	8.5 (1.94)

Note: Data are mean (SD) unless otherwise stated.
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; N, number of participants with nonmissing data; PPG, postprandial glucose.

Type 2 Diabetes Mellitus),[10] and NCT01175824 (Comparison of the Efficacy and Safety of Two Insulin Intensification Strategies).[11]

Key characteristics from the individual trials are presented in Table 2. A total of 1572 patients were included in the analyses. Population characteristics were generally similar across trials: the mean age ranged between 54 and 60 years, duration of diabetes between 10 and 15 years, and baseline HbA1c between 67.4 and 78.9 mmol/mol (8.32% and 9.37%). The mean body mass index ranged from 26 to 35 kg/m^2 and baseline TIR from 30% to 62%. The mean change from baseline HbA1c was −14.3 ± 12.9 mmol/mol (−1.31% ± 1.18%), with an endpoint of 55.8 ± 11.3 mmol/mol (7.26% ± 1.03%). The mean FPG at endpoint was higher than the target in all the studies included (Table 2).

3.2 | Association between FPG and HbA1c and PPG and HbA1c

Results of the pooled analysis and the mean change from baseline values for FPG, PPG and HbA1c are shown in Figure 1. The pooled analysis showed a significant association between change in FPG and change in HbA1c: a 1-mmol/L increase in FPG was associated with a 2.7 mmol/mol (0.25%) increase in HbA1c (P <0.0001; Figure 1A). The coefficient estimates from each study ranged from 2.0 to 2.8 mmol/mol (0.18% to 0.26%). Similar results were achieved in the sensitivity analysis: a 1-mmol/L increase in FPG resulted in a 2.8 mmol/mol (0.26%) increase in HbA1c (range 2.1 to 3.1 mmol/mol [0.19%–0.28%]; P <0.0001). The pooled analysis also showed a significant association between change in PPG and change in HbA1c: a 1-mmol/L increase in PPG was associated with a 1.8 mmol/mol (0.16%) increase in HbA1c (range 1.2 to 2.1 mmol/mol [0.11%–0.19%]; P <0.0001 [Figure 1B]). This was also confirmed with the sensitivity analysis, showing a 2.0 mmol/mol (0.18%) increase in HbA1c (range 1.5-2.6 mmol/mol [0.14%–0.24%]) for a 1-mmol/L increase in PPG, all P <0.0001. There was no specific trend of increasing or decreasing FPG or PPG contribution to the change in HbA1c when comparing coefficient estimates across the five studies.

3.3 | Association between FPG and %TIR and PPG and %TIR

Figure 2 shows the results of the pooled analysis, the coefficient estimates from each study, and the mean change from baseline values for FPG, PPG and %TIR. The pooled analysis showed a significant

association between change in FPG and change in %TIR: a 1-mmol/L reduction in FPG was associated with a 6.5% increase in %TIR (ranges from 5.8% to 9.2%; P <0.0001 [Figure 2A]). Similar results were achieved in the sensitivity analysis: a 1-mmol/L reduction in FPG resulted in a 7.1% increase in %TIR (range 6.2%–9.8%; P <0.0001). A significant association was also confirmed between change in PPG and change in %TIR: a 1-mmol/L reduction in PPG was associated with a 5.3% increase in %TIR, with analyses results from individual studies ranging from 4.1% to 8.7% (all P <0.0001; Figure 2B). Sensitivity analyses showed a slightly greater increase in %TIR per 1-mmol/L reduction in PPG (mean 6.6%, range 5.0%–10.0%).

3.4 | Association between %TIR and HbA1c

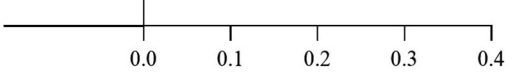
Figure 3 shows the pooled analysis results for the association between change in %TIR and change in HbA1c. For every 10.9 mmol/mol (1%) reduction in HbA1c, %TIR increased on average by 8.3%. Individual study analysis showed this association ranged from 4.6% to 10.2%. Study NCT01175824, which had the highest average %TIR at baseline and the least improvement in both %TIR and HbA1c at endpoint, had the lowest association between %TIR and HbA1c.

4 | DISCUSSION

The analyses from this large type 2 diabetes dataset confirm that metrics commonly used to define hyperglycaemia such as FPG, PPG and %TIR, are associated with HbA1c. In this article we reported the first ever analysis of the association between FPG and PPG with HbA1c and that of FPG and PPG with %TIR in patients with type 2 diabetes on a basal-bolus or basal-plus insulin regimen. Our findings showed that there is an association between FPG and HbA1c and between PPG and HbA1c: a 1-mmol/L increase in FPG was associated with a

(A)

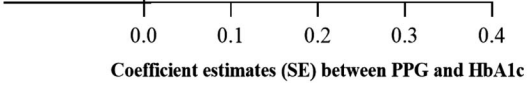
Study	Coefficient Estimate (SE)	*P* value	Change from Baseline HbA1c (mmol/mol), mean (SD)	Change from Baseline FPG (mmol/L), mean (SD)
NCT00110370	0.18 (0.029)	<0.0001	-23.7 (12.4)	-1.7 (3.33)
NCT00377858	0.21 (0.031)	<0.0001	-23.9 (13.8)	-3.8 (2.63)
NCT01215955	0.20 (0.019)	<0.0001	-11.8 (11.6)	0.1 (1.95)
NCT01175811	0.26 (0.035)	<0.0001	-12.2 (11.8)	-1.4 (2.11)
NCT01175824	0.18 (0.044)	<0.0001	-11.2 (11.4)	-0.2 (1.74)
Overall	0.25 (0.011)	<0.0001	-14.3 (12.9)	-0.8 (2.56)



Coefficient estimates (SE) between FPG and HbA1c

(B)

Study	Coefficient Estimate (SE)	*P* value	Change from Baseline HbA1c (mmol/mol), mean (SD)	Change from Baseline PPG (mmol/L), mean (SD)
NCT00110370	0.11 (0.028)	0.0002	-23.7 (12.4)	-5.9 (3.64)
NCT00377858	0.14 (0.033)	<0.0001	-23.9 (13.8)	-4.5 (3.18)
NCT01215955	0.15 (0.014)	<0.0001	-11.8 (11.6)	-2.7 (2.53)
NCT01175811	0.19 (0.031)	<0.0001	-12.2 (11.8)	-2.7 (2.55)
NCT01175824	0.12 (0.039)	0.0033	-11.2 (11.4)	-1.8 (1.92)
Overall	0.16 (0.010)	<0.0001	-14.3 (12.9)	-3.1 (2.88)



Coefficient estimates (SE) between PPG and HbA1c

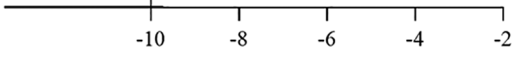
FIGURE 1 Forest plots showing the coefficient estimates (standard error [SE]) between fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) (A) and postprandial glucose (PPG) and HbA1c (B) for the five studies and pooled data, as assessed using the primary model. SD, standard deviation

2.7 mmol/mol (0.25%) increase in HbA1c, while a 1-mmol/L increase in PPG was associated with 1.8 mmol/mol (0.16%) increase in HbA1c. These results are similar to those previously reported by Valensi et al[12] in a post hoc analysis of the IMPROVE study. Although in their study, in contrast to the present study, only breakfast PPG was assessed and patients were treated with premixed insulin therapy, Valensi et al found that a 1-mmol/L decrease in FPG was associated with an absolute reduction in HbA1c of 3.0 mmol/mol (0.27%) and a 1-mmol/L reduction in PPG was associated with an absolute HbA1c reduction of 1.9 mmol/mol (0.17%).[12] These findings suggest that FPG is more closely associated with HbA1c than PPG in patients with type 2 diabetes on basal and bolus insulin therapy. It can therefore be argued that targeting FPG with the goal of improving HbA1c may have a greater impact than targeting PPG. However, improving FPG alone will be insufficient, given that changes in PPG also have a significant impact on changes in HbA1c. This significant association between PPG and HbA1c reinforces the need for clinicians to use a more holistic approach of targeting both FPG and PPG in order to achieve better HbA1c outcomes.

Baseline HbA1c was similar across studies, ranging from 67.4 to 78.9 mmol/mol (8.32% to 9.37%). Comparison of the coefficient estimates among the five studies did not reveal a trend of increasing or decreasing FPG or PPG contribution relative to the change in HbA1c, which may have been due to similar baseline HbA1c across studies within the specified range. This is consistent with an earlier study that found that contributions of PPG and FPG to HbA1c are roughly equivalent with HbA1c levels between 56.3 and 78.1 mmol/mol (7.3% and 9.3%).[2] However, the present results are different from those of a recent meta-analysis by Ketema et al,[13] which suggested a greater association between PPG and HbA1c than between FPG and HbA1c. One could speculate that these differences stem from differences in the treatment method, study design, definition of PPG, and/or analysis methods employed in the various studies. A majority of studies included in the meta-analysis were in patients on oral antidiabetic

(A)

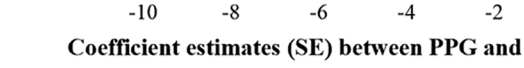
Study	Coefficient Estimate (SE)	*P* value	Change from Baseline TIR (%), mean (SD)	Change from Baseline FPG (mmol/L), mean (SD)
NCT00110370	-5.8 (0.54)	<0.0001	39.5 (25.7)	-1.7 (3.33)
NCT00377858	-8.9 (0.54)	<0.0001	42.3 (31.3)	-3.8 (2.63)
NCT01215955	-6.5 (0.53)	<0.0001	34.2 (28.4)	0.1 (1.95)
NCT01175811	-8.5 (0.61)	<0.0001	26.2 (25.5)	-1.4 (2.11)
NCT01175824	-9.2 (0.64)	<0.0001	18.6 (22.3)	-0.2 (1.74)
Overall	-6.5 (0.25)	<0.0001	32.5 (28.3)	-0.8 (2.56)



Coefficient estimates (SE) between FPG and TIR

(B)

Study	Coefficient Estimate (SE)	*P* value	Change from Baseline TIR (%), mean (SD)	Change from Baseline PPG (mmol/L), mean (SD)
NCT00110370	-4.1 (0.52)	<0.0001	39.5 (25.7)	-5.9 (3.64)
NCT00377858	-6.0 (0.60)	<0.0001	42.3 (31.3)	-4.5 (3.18)
NCT01215955	-4.5 (0.39)	<0.0001	34.2 (28.4)	-2.7 (2.53)
NCT01175811	-7.2 (0.53)	<0.0001	26.2 (25.5)	-2.7 (2.55)
NCT01175824	-8.7 (0.57)	<0.0001	18.6 (22.3)	-1.8 (1.92)
Overall	-5.3 (0.24)	<0.0001	32.5 (28.3)	-3.1 (2.88)



Coefficient estimates (SE) between PPG and TIR

FIGURE 2 Forest plots showing the coefficient estimates (standard error [SE]) between fasting plasma glucose (FPG) and time in range 3.9 to 10.0 mmol/L (TIR) (A) and postprandial glucose (PPG) and TIR (B) for the five studies and pooled data, as assessed using the primary model. SD, standard deviation

agents.[13] While it is not immediately clear, it could be that the patient population in their analysis had more apparent insulin resistance, as seen in patients at earlier stages of diabetes treated with oral antidiabetic agents, rather than insulin deficiency where insulin therapy is initiated, which may have impacted results differently.

Regarding the association between FPG/PPG and %TIR, results showed both measures of glycaemia to have a significant impact on % TIR: a 1-mmol/L reduction in FPG was associated with a 6.5% increase in TIR, while the same reduction in PPG was associated with an increase in TIR of 5.3%. Sensitivity analyses showed a slightly greater increase in %TIR for every 1-mmol/L reduction in FPG and PPG, respectively. Unlike with HbA1c, the impacts of FPG and PPG on TIR were relatively similar, implying that for clinical management PPG control is as important as FPG control for attaining desired TIR outcomes in patients with type 2 diabetes on basal and bolus insulin therapy. In our analysis, %TIR was derived from five to seven blood glucose values per day, which is far less than the 288 data points per day obtained from CGM. Given that similar %TIR results have been achieved when comparing CGM-derived with blood glucose-derived measurements in earlier studies,[14,15] it is reasonable to assume that the association between FPG/PPG and %TIR from SMBG translates to a similar association with %TIR from CGM. However, a recent pooled analysis showed that percentage of time in all glycaemic ranges reported by SMBG and CGM differed significantly, with a higher median %TIR shown with CGM compared with SMBG: 63.0% versus 54.6%, respectively (P <0.001).[16] It is therefore possible that the true extent of the association between either or both measures of glycaemia and %TIR may not have been adequately captured with the analysis employed in the present study. In addition, a large percentage of patients in the analysis set were not treated to FPG goals, which may have impacted the analysis results of the contribution of PPG to %TIR. Still, it is encouraging to see that improvements in both FPG and PPG impact %TIR significantly, suggesting that therapeutics that demonstrate improved FPG and PPG control may be beneficial in achieving increased TIR. Our analysis showed that an average decrease in FPG or PPG of ~1 mmol/L may result in an increase in %TIR of ≥5%, an increment associated with clinically significant benefits for individuals with type 1 or type 2 diabetes.[17] In the post hoc analysis of data from the DCCT trial, Beck et al[4] found that the development of retinopathy and microalbuminuria increased significantly with decreases in TIR: the hazard rate of development of retinopathy progression and microalbuminuria was increased by 64% and 40%, respectively, for each 10-percentage-points lower TIR (P <0.001 for both). Similarly, in another study evaluating associations between CGM data and pregnancy outcomes, less time in target range was associated with increased risk of large-for-gestational-age infants and an adverse neonatal composite outcome.[18] Therapies that improve FPG and/or PPG significantly, have an impact on HbA1c and TIR and therefore have the potential to improve clinical outcomes for individuals with diabetes.

The final analysis looked at the relationship between TIR and HbA1c. Baseline and endpoint %TIR to HbA1c followed similar trends to those previously described,[5] with higher %TIR generally corresponding with lower HbA1c. Results demonstrated a strong association between %TIR and HbA1c, with TIR increasing by 8.3% on average for every 10.9 mmol/mol (1%) reduction in HbA1c. This was similar to results demonstrated by Vigersky and McMahon[19] in an analysis of 18 randomized controlled trials encompassing over 2500 individuals with type 1 and 2 diabetes using both CGM- and SMBG-derived %TIR. In their analysis, for every absolute 10% change in TIR, there was a 8.8 mmol/mol (0.8%) change in HbA1c. Another study analysing datasets from four randomized trials, showed that an increase in TIR by 10% corresponded with a decrease in HbA1c of approximately 6.6 mmol/mol (0.6%).[5] Again, it should be noted that differences in derivation of %TIR (CGM vs. SMBG) and the various methods of calculating %TIR could impact results.

A limitation of this study is the use of SMBG data, which inherently limits the quantity of data that can be used to estimate %TIR.

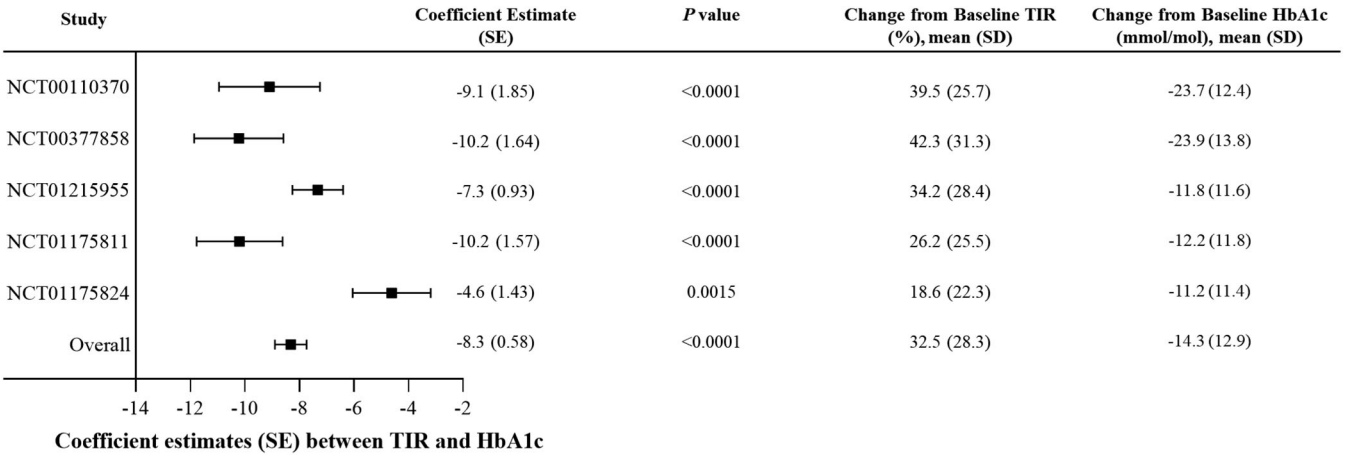


FIGURE 3 Forest plot showing the coefficient estimates (standard error [SE]) between time in range 3.9 to 10.0 mmol/L (TIR) and glycated haemoglobin (HbA1c) for the five studies and pooled data. SD, standard deviation

The possibility that SMBG-derived TIR may under- or overestimate true TIR could affect our calculation of the relationships between TIR and HbA1c and between PPG/FPG and TIR. While our findings generally follow trends in the literature, it would be of interest to assess the associations between glycaemia metrics and %TIR in a trial where CGM is mandated, as CGM data may provide more robust estimates of TIR. Similarly, PPG data from SMBG provides only point estimates of glucose excursion and may not represent the full spectrum of the glucose excursion following meals as would be possible with analysing the incremental area under the concentration-time curve. This could have impacted the estimate of PPG contribution to HbA1c and/or TIR. A further limitation is that, although all patients were on intensive insulin therapy, it is not known whether the extent of insulin resistance and/or insulin deficiency was similar among patients, which could potentially impact findings related to both FPG and PPG. Further studies in patients with defined insulin sensitivity may help better assess the extent of the contributions of PPG to HbA1c and to TIR. Finally, although it was not possible to analyse the impact of race/ethnicity and age on the relationships among the glycaemic metrics in this study due to the relatively homogenous sample, it would be of interest for future studies to perform such analyses as these population characteristics may play an important role in red blood cell survival and potentially impact HbA1c.

In the present study, we demonstrated that both FPG and PPG have a significant impact on HbA1c in patients with type 2 diabetes on basal and bolus insulin regimens, with FPG having greater implications for HbA1c outcomes. While HbA1c continues to be an important measure of long-term glycaemic control, a significant number of patients continue to fail to meet or maintain HbA1c targets, which can be more apparent when diabetes management only focuses on one metric instead of both FPG and PPG control. This study reinforces the importance of daily glucose management of both FPG and PPG in order to achieve those long-term glycaemic goals in this demographic. We also demonstrated that improvements in both FPG and PPG of approximately 1 mmol/L can result in clinically relevant improvements in TIR and that PPG control is as important as FPG control for attaining improved TIR outcomes. We conclude that for patients with type 2 diabetes on basal-bolus or basal-plus insulin regimens, it is important to continue monitoring changes in both FPG and PPG to ensure that patients achieve long- and short-term glycaemic goals of improved HbA1c and TIR.

ACKNOWLEDGMENTS

The authors thank Drs Jacek Kiljanski and Mary Anne Dellva (Eli Lilly and Company, Indianapolis, Indiana) for critically reviewing the manuscript. This study and the studies included in the pooled analysis were funded by Eli Lilly and Company.

CONFLICT OF INTEREST

B.L., F.C. and C.P.O. are employees and shareholders of Eli Lilly and Company. Y.C. is an employee of Techdata Service Company, LLC and has provided consulting services to Eli Lilly and Company. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

B.L. and C.P.O. contributed to the design of the study. Y.C. contributed to the data collection and statistical analysis of the study. F.C. contributed to the interpretation of data and writing of the manuscript. All authors were involved in writing, reviewing, and finalization of the manuscript. All authors approved the final manuscript to be published. C.P.O. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14370.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Liao B, Chen Y, Chigutsa F, Piras de Oliveira C. Fasting and postprandial plasma glucose contribution to glycated haemoglobin and time in range in people with type 2 diabetes on basal and bolus insulin therapy: Results from a pooled analysis of insulin lispro clinical trials. *Diabetes Obes Metab*. 2021;23:1571–1579. https://doi.org/10.1111/dom.14370