Hypoglycaemia in type 2 diabetes treated with pre-mixed insulin

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LETTER

Hypoglycaemia in type 2 diabetes treated with pre-mixed insulin

The burden of hypoglycaemia in type 2 diabetes is increasingly recognised, regardless of the treatment regimen.[1–3] However, time in hypoglycaemia for individuals with type 2 diabetes who use pre-mixed (biphasic) insulin remains unclear. The aim of our prospective, open-label, single arm, pilot, observational study was to determine the amount of time individuals in this cohort spent in hypoglycaemia (ISRCTN 10603608). The primary endpoint was sensor derived time in hypoglycaemia (TBR, <3.9 mmol/L). Secondary endpoints included; time above range (TAR, >10.0 mmol/L), time in range (TIR, 3.9–10.0 mmol/L), standard deviation (SD), coefficient of variation (CV) glucose, and estimated A1c (calculated from sensor glucose data). Eligible participants were adults with type 2 diabetes on pre-mixed insulin for ≥6 months prior to enrolment with an HbA_{1c} <58 mmol/mol (7.5%). HbA_{1c} was measured at baseline (day 1) and study end (day 14). Participants wore a professional continuous glucose monitoring (CGM) system (FreeStyle Libre Pro® Abbott, Diabetes Care) for 14 days continuing usual daily activities and using their personal device for self-monitoring of blood glucose (SMBG). Sensors were removed and sensor data were uploaded for study outcomes analysis and were not clinically reviewed. Informed, written consent was given by all participants.

Data from 12 study sites (eight primary, four secondary care) and 41 individuals (n = 41/43, 2 sensors collecting <72 h of data were excluded) were used for glycaemic analysis and from 43 individuals for the safety analysis. Baseline values for study participants were; age 68.8 ± 8.3 years, HbA_{1c} 52 ± 8.3 mmol/mol (6.9 ± 0.8%), BMI 35.0 ± 9.2 kg/m^2, pre-mixed insulin use duration 6.8 ± 4.8 years, 65.1% (28/43) participants used non-insulin anti-diabetes medication, SMBG testing 1.9 ± 1.1/day and 65.1% were males (mean ± SD).

TBR (<3.9 mmol/L) was 1.35 ± 1.56 h/day (mean ± SD [median 0.66]) including 0.82 ± 1.06 at night (23:00 to 06:00). TBR occurred in 34 (82.9%) participants and TBR >1 h/day (4%) in 17 (41%) participants (Table 1). TBR was associated with baseline HbA_{1c} <53 mmol/mol (7%) compared to >53 mmol/mol (7%), p-value, multiway ANOVA, 0.006. No association with TBR for age (<65 and ≥65 years), BMI (<30 kg/m^2 and ≥30 kg/m^2), duration of diabetes (<16 and ≥16 years), sex, higher daily insulin doses, and insulin units/kg of body weight was observed.

Mean TIR was 19.1 h/day (79.6%); 13.3 h (78.5%) during waking hours (06:00 to 23:00) and 5.8 h (82.2%) at night, <70% TIR was observed in 7 (17%) participants. Mean TAR (>10.0 mmol/L) was 3.55 h/day including 3.15 h during waking hours, >25% TAR was observed in 8/41 (20%) participants. For glucose variability, mean SD was 2.3 mmol/L, (2.2 mmol/L day, 1.8 mmol/L night) while CV was 31.2% and similar during day/night.

Study end HbA_{1c} was 52 ± 7.6 mmol/mol (mean ± SD [6.9 ± 0.7%]). Overall, estimated A1c was 44 mmol/mol (6.2%), 47 mmol/mol (6.5%) for daytime and 37 mmol/mol (5.6%) at night. Glucose Management Indicator was 6.5% (47 mmol/mol) overall, 6.6% (49 mmol/mol) daytime and 6.0% (42 mmol/mol) nighttime).

There were no serious adverse or unanticipated adverse events related to the device or study procedure. The minimal mild symptoms relating to sensor insertion/wear were typical of medical adhesive use in diabetes technology.

Knowledge of clinically applicable CGM glycaemic metrics arising from pre-mixed insulin use are largely unreported outside of efficacy and safety trials. International Consensus Guidelines for Time in Range (IC-TiR) recommended an optimal percentage of time spent in, above or below range.[4] Our analysis revealed a mean TBR of 81 min day (5.6%), higher than the IC-TiR recommended ≤60 min (4%). Comparative reported hypoglycaemia data in a similar population with CGM are sparse.[5–7] A 2015 meta-analysis of population-based studies of type 2 diabetes (excluding pharmacological trials) reported a prevalence of 45% for mild/moderate hypoglycaemia in type 2 diabetes with insulin treatment, broadly similar to the global HAT study (>46.5%)[1,2] In the current study, almost 83% of participants spent time in level 1 hypoglycaemia[4] most of which (60% or 49 min) was at night (23.00–06.00 h). The findings from the recent global HAT study[2] confirmed

TABLE 1 Glycaemic measures

Glycaemic measure	24 h	Day (06:00–23:00)	Night (23:00–06:00)
Time spent (h/day) <3.9 mmol/L			
Mean	1.35	0.51	0.82
SD	1.56	0.62	1.06
25th percentile	0.13	0.02	0.04
Median	0.66	0.29	0.25
75th percentile	2.01	0.93	1.45
95% confidence interval	0.85 to 1.84	0.31 to 0.71	0.49 to 1.16
Time spent (%) <3.9 mmol/L			
Mean	5.6	3.0	11.8
SD	6.5	3.6	15.1
25th percentile	0.5	0.1	0.5
Median	2.8	1.7	3.6
75th percentile	8.4	5.5	20.7
95% confidence interval	3.6 to 7.7	1.8 to 4.1	7.0 to 16.5
Time spent (h/day) <3.0 mmol/L			
Mean	0.02	0.00	0.01
SD	0.05	0.02	0.05
25th percentile	0.00	0.00	0.00
Median	0.00	0.00	0.00
75th percentile	0.00	0.00	0.00
95% confidence interval	0.00 to 0.03	0.00 to 0.01	0.00 to 0.03
Time spent (%) <3.0 mmol/L			
Mean	0.1	0.0	0.2
SD	0.2	0.1	0.6
25th percentile	0.0	0.0	0.0
Median	0.0	0.0	0.0
75th percentile	0.0	0.0	0.0
95% confidence interval	0.0 to 0.1	0.0 to 0.1	0.0 to 0.4
Time spent (h/day) >10 mmol/L			
Mean	3.55	3.15	0.42
SD	3.07	2.83	0.51
25th percentile	1.29	1.09	0.00
Median	2.58	2.02	0.22
75th percentile	4.97	4.52	0.54
95% confidence interval	2.58 to 4.52	2.25 to 4.04	0.26 to 0.58
Time spent (%) >10 mmol/L			
Mean	14.8	18.5	6.0
SD	12.8	16.7	7.3

(Continued)

TABLE 1 (Continued)

Glycaemic measure	24 h	Day (06:00–23:00)	Night (23:00–06:00)
25th percentile	5.4	6.4	0.0
Median	10.8	11.9	3.1
75th percentile	20.7	26.6	7.7
95% confidence interval	10.8 to 18.8	13.3 to 23.8	3.7 to 8.3
Time in range (h/day) 3.9–10 mmol/L			
Mean	19.1	13.3	5.8
SD	3.0	2.7	1.1
25th percentile	17.9	12.1	5.3
Median	19.8	14.2	6.1
75th percentile	21.4	15.3	6.6
95% confidence interval	18.2 to 20.0	12.5 to 14.2	5.4 to 6.1
Time in range (%) 3.9–10 mmol/L			
Mean	79.6	78.5	82.2
SD	12.4	15.8	15.2
25th percentile	74.5	71.4	75.4
Median	82.6	83.4	86.8
75th percentile	89.1	89.8	93.7
95% confidence interval	75.7 to 83.5	73.5 to 83.5	77.4 to 87.0
Mean glucose (mg/dl)			
Mean	131.8	139.6	113.0
SD	22.2	25.2	21.9
25th percentile	117.2	122.2	94.8
Median	129.4	131.9	113.7
75th percentile	145.6	151.3	130.9
95% confidence interval	124.8 to 138.8	131.7 to 147.6	106.1 to 119.9
Mean glucose (mmol/L)			
Mean	7.3	7.7	6.3
SD	1.2	1.4	1.2
25th percentile	6.5	6.8	5.3
Median	7.2	7.3	6.3
75th percentile	8.1	8.4	7.3
95% confidence interval	6.9 to 7.7	7.3 to 8.2	5.9 to 6.7

that hypoglycaemia may be present at any level of glucose control.[8] Our findings are especially pertinent in this older cohort at increased risk of hypoglycaemia. The IC-TiR recommendation is <15 min or 1% TBR in 24 h for these individuals.[4]

Observed CV was within the IC-TiR recommended target,[4] however, both CV and SD of glucose are higher than reported findings for basal bolus insulin use in type 2 diabetes.[9,10]

The difference in the observed HbA_{1c} and eA1c values should be interpreted with caution as the eA1c measurement was calculated using CGM data during the 14-day sensor wear. Although these two measurements may not exactly concur, previous studies have reported reasonable correlations, with eA1c value being clinically useful and offering an awareness of trends and what a future laboratory-measured HbA_{1c} might be.[11,12]

The generalisability of findings is restricted to well-controlled type 2 diabetes managed with a biphasic insulin regimen, 65.1% of whom were also receiving non-insulin anti diabetes medication. The impact of bi-phasic insulin and non-insulin anti-diabetes medication on glucose profile

and patterns were, however, not able to be analysed due to the observational nature of this study and hence outside the remit of this study. However, the inclusion of primary and secondary care sites utilising biphasic insulin within routine practice highlights the potential ease of CGM technology utilisation in specialist and non-specialist clinics.

Our finding highlights a continuing risk of level 1 hypoglycaemia in individuals with type 2 diabetes using premixed insulin and who have an HbA_{1c} at target levels. The use of professional or real-time CGM may be an invaluable tool to identify hypoglycaemia risk and review treatment in this population.

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REFERENCES

1. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and incidence of hypoglycemia in 532,542 people with type 2 diabetes on oral therapies and insulin: a systematic review and meta-analysis of population based studies. *PLoS ONE*. 2015;10(6):e0126427. doi:10.1371/journal.pone.0126427
2. Khunti K, Alsifri S, Aronson R, et al. Rates and predictors of hypoglycemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab*. 2016;18(9):907-915.
3. Dunkley AJ, Fitzpatrick C, Gray LJ, et al. Incidence and severity of hypoglycaemia in type 2 diabetes by treatment regimen: a UK multisite 12-month prospective observational study. *Diabetes Obes Metab*. 2019;21(7):1585-1595.
4. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593-1603.
5. Ajjan RA, Jackson N, Thomson SA. Reduction in HbA1c using professional flash glucose monitoring in insulin-treated type 2 diabetes patients managed in primary and secondary care settings: a pilot, multicentre, randomised controlled trial. *Diab Vasc Dis Res*. 2019;16(4):385-395.
6. Furler J, O'Neal D, Speight J, et al. Use of professional-mode flash glucose monitoring, at 3-month intervals, in adults with type 2 diabetes in general practice (GP-OSMOTIC): a pragmatic, open-label, 12-month, randomised controlled trial. *Lancet Diabetes Endocrino*. 2020;8:17-26.
7. Li F-F, Fu L-Y, Zhang W-L, et al. Blood glucose fluctuations in type 2 diabetes patients treated with multiple daily injections. *J Diabetes Res*. 2016;2016:1028945. doi:10.1155/2016/1028945
8. Cariou B, Fontaine P, Eschwege E, et al. Frequency and predictors of confirmed hypoglycaemia in type 1 and insulin-treated type 2 diabetes mellitus patients in a real-life setting: results from the DIALOG study. *Diabetes Metab J*. 2015;41:116-125.
9. Bellido V, Suarez L, Galiana Rodriguez M, et al. Comparison of basal-bolus and premixed insulin regimens in hospitalised patients with type 2 diabetes. *Diabetes Care*. 2015;38:2211-2216.
10. Monnier L, Colette C, Wojtusciszyn A, et al. Toward defining the threshold between low and high glucose variability in diabetes. *Diabetes Care*. 2017;40(7):832-838.
11. Bergenstal RM, Beck RW, Close KL, et al. Glucose Management Indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. *Diabetes Care*. 2018;41(11):2275-2280. doi:10.2337/dc18-1581
12. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. *J Diabetes Sci Technol*. 2019;13:614-626. doi:10.1177/1932296818822496