Impaired awareness of hypoglycaemia; prevalence and associated factors before and after FreeStyle Libre use in the Association of British Clinical Diabetologists (ABCD) audit

Short running title: Impaired awareness of hypoglycaemia and FSL

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Word count manuscript: 1325 words

Number of tables and figures: 2

Background

FreeStyle Libre (FSL), intermittently scanned continuous glucose monitoring (isCGM), is associated with less biochemical hypoglycaemia in people with diabetes, lower HbA1c and diabetes-related distress[1]. Impaired awareness of hypoglycaemia (IAH), which affects between 18-33% of people with type 1 diabetes[2], is the reduced ability to detect the symptoms of hypoglycaemia and is associated with a 6-fold increased risk of severe hypoglycaemia[3]. Many of the studies of CGM have shown a reduction in rates of hypoglycaemia but have not demonstrated restoration of awareness[4–6].

There is limited nationwide data investigating the prevalence of IAH, complete loss of awareness of hypoglycaemia and severe hypoglycaemia (SH). We have recently shown the use of FSL is associated with improvement in awareness of hypoglycaemia[1], however, some studies have shown no benefit of FSL on IAH[5,7]. It is therefore important to identify the factors associated with improvement in IAH with the use of FreeStyle libre.

Methods

This observational study analysed data collated from November 2017 to August 2021 as part of the nationwide Associations of British Clinical Diabetologists (ABCD) audit on FreeStyle libre[8]. The methodology of the nationwide audit has been described in an article[1] reporting previous results of the audit. In this audit people with diabetes were using FreeStyle libre or FreeStyle Libre 2.

The Gold score was used to assess awareness of hypoglycaemia[9]. A score of ≥4 indicates IAH and 7 indicates complete loss of awareness[9]. Diabetes-related distress was measured using the two–item diabetes distress screening tool (DDS2).[10] An average of the two questions of the DDS2 scale was calculated. A score of ≥3 was classified as “moderate diabetes-related distress” and an average score of < 3 was considered as “low distress”.

Statistical analysis was performed using SPSS statistics, version 27 for Mac. All people aged 18 years and over with at least one follow-up visit after FSL initiation were included in the analysis. The total

number of SH episodes were reported per month. Multiple logistic regression was performed to explore factors associated with improvement in awareness of hypoglycaemia with the use of FSL.

Results

Supplementary Table 1 shows baseline demographic and clinical characteristics for the entire study population, 14248 people living with diabetes and 4391 people with paired baseline and follow-up Gold scores. The mean follow-up time was 7.6 months. The baseline demographic characteristics were very similar for the entire study population and people with paired baseline and follow-up Gold scores. Half (51.2%) were female, with a median age of 46 years (32-57) and a median diabetes duration of 21 years (11-34). Most people had type 1 diabetes, 98.2%, 21.4% used continuous subcutaneous insulin infusion (CSII). 64.7% of the cohort had completed structured diabetes education. The average pre-FSL HbA1c was 68.7 (±18.8) mmol/mol (8.7%). The mean diabetes related distress score (DDS) was 3 (±1.3). The total number of severe hypoglycaemic episodes was 464 per month at baseline for the entire study population.

With the use of FSL, the prevalence of IAH reduced from 28.1% at baseline to 18.1% at follow-up **(Figure 1).** The mean Gold score reduced from 2.6 (±1.7) at baseline to 2.3 (±1.6) after FSL use (P<0.001). The percentage of people with complete loss of awareness decreased from 3.7% to 3.2%. The total number of SH episodes across the cohort decreased from 140 per month to 48 per month at follow-up. The prevalence of people with at least one episode of SH reduced from 14.4% to 4.7%.

The prevalence of experiencing at least one SH episode was greater for people with IAH, 37.2% compared to 11.1% (P<0.001), an almost 4-fold increased risk. Just over half (54.6%, (673/1233) of people with IAH at baseline, had restoration of awareness of hypoglycaemia (Gold score <4) at follow-up. The prevalence of IAH reduced from 54.1% at baseline to 33.1% at follow-up for people who experienced ≥1 SH at baseline.

The univariate analysis (**Supplementary table 2**) showed that people who had restoration of awareness following initiation of FSL had a higher time in range (TIR) 48.6% (±19.9), compared to those who continued to have IAH 44.9% (±19) (P=0.002) and a shorter duration of diabetes (P<0.001). A higher proportion of people with restoration of awareness had a time below range (TBR) <4%, 44.4% compared to 36.7% of people who did not have restoration of awareness (P=0.011).

Table 1 shows results for multiple logistic regression analysis that explored factors associated with restoration of awareness with the use of FSL. 1285/4391 people had a TIR reported between the international consensus guidelines of 3.9-10mmol/L. 531 people with paired baseline and follow-up Gold score, with TIR 3.9-10mmol/L were included in the regression analysis. People with a TIR between 3.9 – 10mmol/L were included in the regression analysis. A longer duration of diabetes was associated with an increased likelihood of having IAH after initiation of FSL [OR:1.030 (95% CI:1.012 - 1.048) P=0.001]. A greater percentage TIR was associated with a decreased likelihood of having IAH at follow-up [OR: 0.982 (95% CI: 0.969 – 0.994) P=0.005]. A greater DDS score was associated with an increased likelihood of having IAH after initiation of FSL. [OR:1.193 (95%:1.014 – 1.403) P=0.033]. A higher baseline Gold score was associated with an increased likelihood of having IAH at follow-up [OR: 1.518 (95% CI:1.230 – 1.872) P<0.001].

Conclusions

We present data exploring the prevalence of IAH and problematic hypoglycaemia in people living with diabetes from the nationwide ABCD audit. The baseline prevalence of IAH and complete loss of awareness of hypoglycaemia reduced from 28.1% to 18.1% and 3.7% to 3.2% respectively. We also demonstrated that just over half of the people with IAH at baseline had restoration of awareness at follow-up, similar to the results reported in a study by Tyndal et al, that showed IAH resolved in 42.5% of people[7]. Our findings demonstrate that FSL can help restore awareness in those with IAH.

There was an almost 4-fold increased risk of severe hypoglycaemia for people with IAH, confirming the established relationship between SH and IAH. Our results also show the beneficial effects of FSL on reducing the total number of SH episodes from 140 per month at baseline to 48 per month at follow-up.

We show that a shorter duration of diabetes and higher proportion of time spent in time in range 3.9-10mmol/L, were associated with restoration of awareness with the use of FSL. Some people in the cohort did not have an improvement in awareness with the use of FSL. This indicates that a combined approach of structured education and diabetes technologies; isCGM, CGM, CSII and closed loop technologies should be considered[11]. Diabetes-related distress, anxiety and depression should also be considered in people with IAH[12].

This study has some limitations. Our results are from data collected as part of routine clinical care and there is no comparator. The data collected were from participants who were eligible for FSL under the NHS criterion, one of which is problematic hypoglycaemia. This may lead to overestimation of the prevalence of severe hypoglycaemia and IAH in this cohort. However, almost half of the people living with T1D had access to FSL when these data were downloaded which increases the generalizability of this study. The number of SH episodes at baseline were recorded in the previous 12 months, whereas the number of SH episodes after FSL use was recorded for a follow-up time of 7.6 months. However, we have reported pro-rata monthly reduction in episodes of SH post-FSL use. The audit data shows there is low uptake of the international consensus TIR of 3.9-10mmol/L, the recommended range should be used more widely in clinical practice.

In this analysis of audit data, the use of FSL appears to be similar in people who have restored awareness and people who continued to have IAH at follow-up. It is likely that restoration of hypoglycaemia awareness depends on multiple factors such as frequency of use of FSL, duration of diabetes, duration of hypoglycaemia unawareness and access to healthcare for insulin optimization following the use of FSL. As some of these variables were not captured in this study, we are not able to adjust for these.

In summary, this large real-world study of predominantly people living with type 1 diabetes shows a high prevalence of problematic hypoglycaemia, impaired awareness of hypoglycaemia and severe hypoglycaemia. The prevalence of both IAH and severe hypoglycaemia significantly reduced after the use of FreeStyle Libre. Just over half of the people with IAH had restoration of awareness of hypoglycaemia after FSL use. Restoration of hypoglycaemia awareness following FSL initiation was associated with a shorter duration of diabetes and greater time in range.

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Tables

Table 1: *Multiple logistic regression analysis with impaired awareness of hypoglycaemia (Gold ≥4) after FSL initiation as the binary outcome. People with IAH at baseline with paired baseline and follow-up Gold score data, with TIR between 3.9 – 10 mmol/L were included in this analysis, mean follow-up time 7.6 months.*

	OR	**95% CI**	***P* value**
Age (years)	0.995	0.979 – 1.012	*P*=0.585
Sex **Female**	1.377	0.895 – 2.118	*P*=0.145
Duration of diabetes (years)	1.030	1.012 – 1.048	*P*=0.001
Ethnicity **Caucasian**	0.610	0.330 – 1.126	*P*=0.114
Baseline Gold score	1.518	1.230 – 1.872	*P*<0.001
Completion of structured diabetes education	1.003	0.646 – 1.557	*P*=0.991
CSII	0.822	0.488 – 1.383	*P*=0.459
Baseline HbA1c (mmol/mol)	0.990	0.974 – 1.005	*P=0.*184
Average DDS at baseline	1.193	1.014 – 1.403	*P*=0.033
FSL scans per day	0.991	0.967 – 1.015	*P*=0.445
Time in range (%)	0.982	0.969 – 0.994	*P*=0.005
Time below range (%)	1.006	0.990 – 1.024	*P*=0.455

Figures

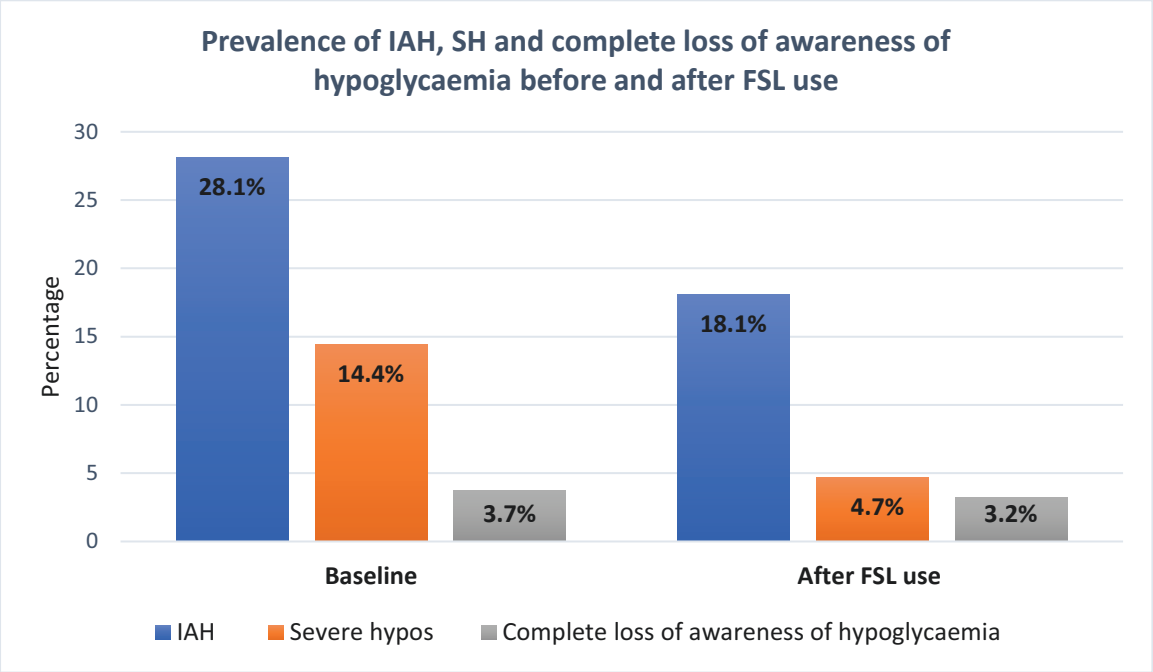

Figure 1: *Bar chart to show prevalence of impaired awareness of hypoglycaemia, severe hypoglycaemia episodes and complete loss of awareness of hypoglycaemia before and after FSL use. A Gold score of <4 indicates normal awareness of hypoglycaemia and a score of ≥4 indicates IAH.*

Author contributions

B.P did the statistical analysis and drafted the manuscript. H.D drafted and reviewed the manuscript. T.S, E.G.W, P.C, D.B, gave constructive feedback and revised the manuscript. E.G.W, P.C, N.S, R.G, D.B, S.S, J.P, C.W, R.E.J.R, T.S reviewed and approved the manuscript. H.D and T.S provided overall supervision of the project. T.S, E.G.W, R.E.J.R, J.P, C.W conceived the nationwide FreeStyle Libre ABCD audit.

Acknowledgements

The authors would like to thank all the clinicians and support staff who participated in the nationwide study, listed at https://abcd.care/Resource/ABCD-Freestyle-LibreAudit-Contributors.

Conflicts of interest

The ABCD nationwide FSL audit is supported by a grant from Abbott Laboratories. E.G.W. serves on the advisory panel for Abbott Diabetes Care, Dexcom, and Eli Lilly and Medtronic; has received research support from Diabetes UK; and is on the speakers bureau for Abbott Diabetes Care, Dexcom, Eli Lilly and Medtronic, Insulet Corporation, Novo Nordisk, and Sanofi. C.W. has a spouse/partner serving on the advisory panel for Celgene and on the speakers bureau for LEO Pharma and Novartis. R.E.J.R. serves on the advisory panel for Novo Nordisk A/S and on the speakers bureau for BioQuest. T.S. is on the speakers bureau for NovoNordisk Foundation and reports a relationship with Bristol-Myers Squibb, Eli Lilly and Company, and Sanofi. H.D is partly funded through the NIHR academic programme. No other potential conflicts of interest relevant to this article were reported. The FSL audit was independently initiated and performed by ABCD, and the authors remain independent in the analysis and preparation of this report.