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Flash glucose monitoring (FGM): A clinical review on glycaemic outcomes and impact on quality of life

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ABSTRACT

Flash glucose monitoring (FGM) is widely accepted as an alternative means to conventional finger prick test for measuring glucose level in individuals with diabetes mellitus. In this clinical review, we endeavour to draw all available clinical evidence on the usage and efficacy of FGM from research trials and observational studies in real-world settings. We aim to explore its clinical efficacy and impact on quality of life (QoL) in the diabetic population. In terms of clinical outcomes, use of FGM is associated with a significant reduction in glycated haemoglobin A1c (HbA1c) level, notably in patients with suboptimal glycaemic control prior to commencement of FGM and reduction in time spent in hypoglycaemia. FGM demonstrated non-inferiority in device accuracy when compared to other well-established CGMs available in the market. Patients have reported improved QoL and treatment satisfaction measured by validated objective scores after consistent use of FGM. This results in a positive impact on patient psychosocial wellbeing and ultimately enhances patient compliance and optimisation of glycaemic control. Evaluation of QoL and patient reported outcome measures (PROMs) will require a standardised approach to allow comparability of the results and evidence.

Contents

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1. Introduction

Good glycaemic control plays a pivotal role in reducing disease burden in diabetes mellitus (DM), with maintenance of normoglycaemia leading to reduced risk of long-term morbidity and mortality.[1,2] Limiting glycaemic variability early on in the disease course reduces the risk of developing DM-associated microvascular and macrovascular complications.[3] However, the balance between optimising glycaemic control while avoiding the risks of the DM treatments can be a challenge for both the patient and the healthcare professional.

To date, self-monitoring of blood glucose (SMBG) has been the gold standard for point-of-care glucose measurement. Current national guidelines for adults with type 1 diabetes mellitus (T1DM) recommend SMBG between four and ten times per day depending on lifestyle.[4,5] However, it is estimated that only 44% of T1DM patients and 24% of type 2 diabetes mellitus (T2DM) patients routinely test as per guidelines[6]; risk factors for poor compliance including fear of blood or needles, stigma of SMBG and DM, perception of SMBG was only for insulin titration, cost and the inconvenience of frequency.[7,8] While SMBG is cheap and readily available it does have some technical limitations, including poor detection of day-to-day glycaemic variability, nocturnal and asymptomatic hypoglycaemia.[9]

Continuous glucose monitoring (CGM) provides an alternative to SMBG.[10] They measure real-time interstitial glucose level and displays data at regular intervals every 1 to 5 min.[9] A systematic review and meta-analysis of four randomised control trials (RCTs) showed a significant reduction in glycated haemoglobin A1c (HbA1c) level in T2DM adults after the use of CGM in comparison with SMBG [mean difference – 0.31% ($p = 0.04$)].[11]The cost of these devices and need for frequent calibration have, unfortunately to date presented barriers to their wider uptake.[12–16]

Flash glucose monitoring (FGM) using devices such as FreeStyle Libre (Abbott Diabetes Care, Witney, UK) have, however, provided an economical alternative to CGM, with readings provided upon scanning of a sensor. FGM functions as a hybrid between SMBG and CGM; patients are able to obtain near real-time glucose levels without the need to finger prick as illustrated in Fig. 1.[17,18] The interstitial fluid glucose level is captured every minute, saved regularly over 15-minute intervals and stored for up to 90 days in a cloud-based system (e.g., LibreViewTM) or personal smartphone (LibreLink app). The analysis of day-to-day trends, frequency/depth and duration of hypoglycaemic events, time in range and the generation of an ambulatory glucose profile (AGP) can enhance individualised diabetes care and direct insulin therapy. The mean absolute relative difference (MARD) of interstitial fluid glucose when compared to capillary glucose has been estimated to be 10%.[19,20] This value is not dissimilar to the MARD of various CGMs which have been reported to be ranging from 9%–13.2%.[21] Moreover, Ji et al. showed that 99.9% of the interstitial glucose measured by FGM and capillary glucose pairs were within the combined zones A and B of the consensus and Clarke error grids.[22] This demonstrated a clinically acceptable accuracy and performance of FGM. FGM is thus widely recognised as a convenient tool for cost-effectiveness blood glucose monitoring.

In January 2018 Leelarathna and Wilmot published a comprehensive clinical review of FGM which provided valuable insight into its use.[23] Since this publication the use of FGM has continued to rise benefiting a wider population, with a number of large-scale observational studies being added to the literature. In this review, we aim to further explore

Fig. 1. A simple illustration of the mechanism of FGM. The factory calibrated FGM sensor which is worn on the upper arm detects interstitial glucose level using a tiny sensor filament underneath the skin. By holding the reader within 4 cm from the sensor, an instantaneous glucose reading is recorded with the trend arrow and AGP made available to the user to guide insulin therapy. Diagram is not drawn to scale. Adapted from https://freestylediabetes.co.uk/freestyle-thinking/post/FreeStyle-Libre-system-measure

Table 1
Summary of randomised controlled trials and observational studies of FGM use on metabolic outcomes and patient reported outcome measures (PROMs).

No	Author	Year	Study design	Sample size	Type of DM	Duration of follow-up	Metabolic outcomes	Patient reported outcome measures (PROMs)
1	Bolinder et al. IMPACT trial[24]	2016	RCT	FGM: 119 Control: 120	T1DM	6 months	38% reduction in time in hypoglycaemia comparing FGM users and control group ($p < 0.0001$). No significant change in HbA1c between both groups at follow up ($p = 0.9543$). Mean number of SMBG reduced from 5.5 ± 2.0 to 0.5 ± 0.7 in FGM users.	No significant difference in DQoL score between both groups ($p = 0.0524$). DTSQ score improved significantly in FGM users ($p < 0.0001$).
2	Haak et al. REPLACE trial[25]	2017	RCT	FGM: 139 Control: 62	T2DM	6 months	50% reduction in time in hypoglycaemia comparing FGM users and control group ($p = 0.0002$). Mean glucose level in FGM users increased from 9.1 mmol/L ± 1.8 (163.3 mg/dL ± 32.7) to 9.4 mmol/L ± 1.5 (169.9 mg/dL ± 27.5) ($p = 0.0409$). Mean number of SMBG reduced from 3.9 ± 1.2 to 0.6 ± 1.2 in FGM users.	
3	Reddy et al.[26]	2017	RCT	FGM: 20 CGM: 19	T1DM	T8 weeks	Median HbA1c in FGM users reduced from 55 mmol/mol (159 mg/dL) to 51 mmol/mol (149 mg/dL). Median percentage time in hypoglycaemia increased from 8.0% (IQR 5.7–10.7) to 8.2% (IQR 6.0–13.2) in FGM users	
4	Yaron et al.[27]	2019	RCT	FGM: 52 Control: 44	T2DM	10 weeks	Significant reduction in HbA1c in FGM users, −0.85% ± 0.45 vs. −0.32% ± 0.39 ($p < 0.0001$). Frequency of hypoglycaemic episodes did not significantly differ between groups.	Mean DTSQc score was 2.47 ± 0.77 (FGM users) vs. 2.18 ± 0.83 (control) ($p = 0.053$). FGM users found it more flexible and would recommend to their counterparts. ADDQoL questionnaires scores were not significant between both groups. WHO-5 ($p < 0.001$) and DTSQ ($p = 0.001$) scores were both significantly improved after use of FGM.
5	Mitsuishi et al.[28]	2018	PC	FGM: 80	T1DM and T2DM	2 weeks		
6	Moreno-Fernandez et al.[29]	2018	RC	FGM: 18 Control: 18	T1DM	24 weeks	Significant change in HbA1c in FGM group −0.4% ($p = 0.004$) as compared to control 0.1% ($p = 0.64$). No significant difference in frequency of hypoglycaemic episodes. Frequency of SMBG per day decreased from 5.2 ± 2.5 to 2.8 ± 1.7 ($p = 0.01$).	
7	Paris et al.[30]	2018	PC	FGM: 120	T1DM	12 months	Significant change in HbA1c from 70 mmol/mol ± 1.5 (198 mg/dL ± 4.0) to 61 mmol/mol ± 10.4 (176 mg/dL ± 27.3) ($p < 0.0001$). Number of hypoglycaemic events per month significantly increased from 16.9 ± 1.44 to 22.9 ± 2.03 ($p < 0.001$).	
8	Heald et al.[31]	2019	PC	FGM: 92	T1DM	3–6 months	Significant change in mean HbA1c from 83 mmol/mol (233 mg/dL) to 72.3 mmol/mol (205 mg/dL) at 3 months ($p < 0.0001$) and 66.9 mmol/mol (191 mg/dL) at 6 months ($p < 0.0001$).	
9	Kramer et al.[32]	2019	PC	FGM: 40	T1DM	12 months	No significant change in HbA1c from 57.6 mmol/mol ± 11.4 (166 mg/dL ± 29.9) to 57.1 mmol/mol ± 7.4 (165 mg/dL ± 19.4) ($p = 0.688$). Frequency of SMBG decreased from 6.7 ± 4.2 to 0.9 ± 1.8 per day ($p < 0.001$). No difference in insulin dosing, number of insulin injection and BMI between baseline and follow-up.	DTSQc score increased by 12.6 ± 5.5 points at follow up.
10	Nana et al.[33]	2019	RC	FGM: 90	T1DM	3–12 months	Significant change in mean HbA1c of −7.29 mmol/mol ± 10.76 (−19.1 mg/dL ± 28.2) ($p < 0.001$). 51.86% reduction in hypoglycaemic episodes ($p < 0.001$) after FGM use. Significant reduction in frequency of SMBG per day ($p < 0.001$).	Significant improvement in abbreviated DDS score at follow up ($p < 0.001$).
11	Overend et al.[34]	2019	PC	FGM: 40	T1DM	6 months		Absence of finger prick test is a major benefit. Patients reported reduction in frequency and severity of hypoglycaemia. Trend arrows were helpful in achieving good glycaemic control. FGM has positive impact on psychological wellbeing and self-esteem.
12	Tyndall et al.[35]	2019	PC	FGM: 750 Control: 518	T1DM	6 months	Median change in HbA1c was −4 mmol/mol (−10.5 mg/dL) ($p < 0.001$). Median number of glucose test strip use per day reduced from 3.8 to 0.6. Median BMI increased by 0.3 kg/m^2 (FGM users) and 0.1 kg/m^2 (control) ($p = 0.027$).	Percentage of patient with HADS depression score of >7 increased from 7.6% to 15.0% ($p < 0.001$). Percentage of patients with HADS anxiety score of >7 increased from 24.9% to 30.9% ($p = 0.028$).
13	Ish-Shalom et al.[36]	2016	Letter	FGM: 31	T1DM and T2DM	12 weeks	Significant reduction of HbA1c in FGM users, −1.33% ± 0.29 ($p < 0.0001$).	All patients were highly satisfied.
14	Dover et al.[37]	2017	Letter	FGM: 25	T1DM	16 weeks	Mean HbA1c decreased significantly from 64 mmol/mol ± 1.5 (183 mg/dL ± 4.0) to 58	Significant reduction in mean DDS score ($p = 0.006$).

(continued on next page)

Table 1 (*continued*)

No	Author	Year	Study design	Sample size	Type of DM	Duration of follow-up	Metabolic outcomes	Patient reported outcome measures (PROMs)
							mmol/mol ± 1.5 (169 mg/dL ± 4.0) (p = 0.001). Episodes of hypoglycaemia reduced from 17 to 12 (p = 0.019).	
15	McKnight et al.[38]	2017	Letter	FGM: 100 Control: 177	T1DM		Significant change in HbA1c, −2.5 mmol/mol (−6.6 mg/dL) (FGM users) vs. -1.0 mmol/mol (−2.6 mg/dL) (control).	
16	Weiss et al.[39]	2018	Letter	FGM: 22	T2DM	2 weeks	Significant change in HbA1c from 71.6 mmol/mol ± 18.6 (203 mg/dL ± 48.8) to 61 mmol/mol ± 13.1 (174 mg/dL ± 34.4) (p = 0.001).	

RCT: Randomised controlled trial; PC: Prospective cohort; RC: Retrospective cohort; FGM: Flash glucose monitoring; CGM: Continuous glucose monitoring; SMBG: Self-monitoring of blood glucose; HbA1c: glycated haemoglobin A1c; BMI: Body mass index; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; GDM: Gestational diabetes; IQR: Inter-quartile range; CI: Confidence interval; DQoL: Diabetes quality of life; DTSQ: Diabetes treatment satisfaction questionnaire; ADDQoL: Audit of diabetes dependent quality of life; DDS: Diabetes distress scale; WHO-5: World Health Organisation well-being index; HADS: Hospital anxiety and depression scale.

the use of FGM and its outcomes both with regards to clinical efficacy and impact on quality of life (QoL) in the diabetic population.

2. Method

2.1. Literature search and eligibility criteria

A systematic search was performed using MEDLINE and EMBASE. Search terms included "flash glucose monitoring", "freestyle libre", "HbA1c", "hypoglycaemia", "diabetes mellitus" and variants, combined using Boolean operators as appropriate. All study designs including RCTs, prospective and retrospective observational studies of FGM use in adults with associated clinical outcomes published in English language were eligible for screening.

2.2. Study selection

Following removal of duplicates, 418 articles were screened independently by two reviewers (EA and ZXL). Conference abstracts and review papers were excluded. Discrepancies were resolved by a third author (SM). 29 selected full-text articles were subsequently reviewed. 13 studies were excluded for reasons including use of professional CGM FreeStyle Libre Pro system, subgroup analysis of an included RCT and paediatric population as study sample. A total of 16 studies were included for data extraction.

2.3. Data extraction and analysis

Data extraction was carried out by two authors (EA and ZXL) independently. Discrepancies were resolved by a third author (SM). The study design, aim, sample size, baseline characteristics and outcomes measures were obtained for each study. The primary outcome assessed was the change in HbA_{1c} associated with FGM use. The secondary outcomes include episodes of hypoglycaemia, frequency of SMBG, time in range, patient reported outcome measures (PROMs) on QoL and adverse events.

3. Current evidence on FGM utilisation

The 16 studies that were included in this review are summarised in Table 1. Four RCTs have provided an insight into FGM technology and its efficacy on glycaemic monitoring; original work by Bolinder et al. and Haak et al. disseminated positive findings on effectiveness in reduction of hypoglycaemic events and SMBG frequency.[24,25] The IMPACT study conducted by Bolinder et al. was the largest multicentre RCT of FGM to date. The study showed a statistically significant mean change in time in hypoglycaemia in the intervention group (−1.39 h/day) compared to the control group (−0.14 h/day) which translates into a 38% reduction in time in hypoglycaemia in T1DM FGM users.[24] In a randomised study performed by Reddy et al., it was concluded that CGM reduces the time spent in hypoglycaemia more effectively than FGM in patients with T1DM.[26] However, the latest RCT published in 2019 by Yaron et al. was the first study demonstrated the beneficial effect of FGM in T2DM population treated with multiple daily insulin injections (MDI). The intervention group had a significant change in HbA1c of −0.82% (9 mmol/mol) in comparison to −0.33% (3.6 mmol/mol) in the control group (p = 0.005). Patients who trialled the FGM technology also had a high treatment satisfaction and found marked flexibility of the treatment.[27] On the other hand, out of the 12 observational studies reported, four were letters, eight were full articles in which six were prospectively conducted and two were retrospective in nature. It is important to note that the current evidence of usefulness of FGM is drawn from T1DM and T2DM treated with insulin therapy. To date, the evaluation of FGM use in non-insulin dependent T2DM has not been assessed.

4. Accuracy of FGM

A highly accurate glucose monitoring device should ensure minimal glucose excursions and prevent adverse outcomes following misinterpretation from false readings. High deviation in glucose readings can have a major clinical impact on insulin dosing errors. With reference to the accuracy of FGM, despite the heterogeneous methodologies in several studies, good accuracy has been reported overall.[19,22,47–50] The MARD of FreeStyle Libre has been evidently stable and narrow within the range of 9.56%–15.4% when it is compared to other methods of glucose measurement (Table 2).[9] Of note, some studies have observed an increased MARD within the first day of application of the sensor but others have described a relatively stable MARD during 14-day study period.[22,47,51,52] Interestingly, Fokkert et al. demonstrated that the site of insertion is also a factor that needs to be considered as attachment of sensor to the upper arm provided reasonably reliable readings while attachment to the abdomen was less valid.[53] Currently, the only approved site of insertion is the upper arm as stated by the manufacturer.[54] In summary, FGM demonstrated non-inferiority compared to other well-established CGMs available in the market in terms of device accuracy. With an overall lower cost of acquisition and no need for daily calibration with SMBG, the uptake of FGM as an alternative to SMBG may rise substantially in the near future.

5. Change in HbA1c

The use of HbA1c in diagnosis and management of diabetes has been widely recognised. One disadvantage of HbA1c is its inability in detecting glycaemic variability or hypoglycaemic events. However, HbA1c is able to reflect the average serum glucose concentration in the preceding

Table 2
Overview of FGM and CGMs available on the market. All data obtained from official manufacturer websites.

	Abbott Freestyle Libre[40]	Dexcom G4® Platinum[41]	Dexcom G5®[42]	Dexcom G6[43]	Sensionics Eversense[44]	Medtronic Enlite Sensor with iPro2[45]	Medtronic GUARDIAN™ Sensor 3[46]
Types	FGM	CGM	CGM	CGM	CGM	CGM	CGM
MARD (%)	9.4	9–13.3	9–13.3	9.8	8.5–9.6	15.6	10.6
Sensor life (days)	14	7	7	10	90	6	7
Attachment site	Upper arm	Abdomen/upper buttock	Abdomen/upper buttock	Abdomen/upper buttock	Upper arm	Abdomen	Abdomen
Requirement for daily calibration	No	Yes	Yes	No	Yes	Yes	Yes

MARD: Mean absolute relative difference; FGM: Flash glucose monitoring; CGM: Continuous glucose monitoring.

8–12 weeks. A tight HbA1c control and reduction in HbA1c value can significantly lower the risk of progression of microvascular complications.[55] As demonstrated in the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), HbA1c has a pivotal role in predicting long-term diabetes-related complications.[56,57] As such, HbA1c is still the gold standard for assessing long-term outcomes of diabetes.[58]

A change in HbA1c has not been reported at six months in the two pioneering RCTs in FGM.[24,25] These findings replicated by Reddy et al. have also demonstrated no statistical change in HbA1c despite numerical improvement in HbA1c level (−4.5 mmol/mol or −2.6%, $p = 0.91$).[26] In contrast, Yaron et al. concluded a significant improvement of HbA1c in the intervention group of insulin-dependent T2DM.[27] Additionally, most observational studies performed in real-world setting have described a significant reduction in HbA1c with FGM use as described in Fig. 2.[29–31,33,35–39] Studies published in 2019 by Heald et al. and Nana et al. reported significant reduction in HbA1c at three months and six months post-FGM use. At six months, the former noted a HbA1c change of −16.1 mmol/mol (−3.6%) and −8.7 mmol/mol (−2.9%) in the latter.[31,33] A large-scale study recently conducted in Scotland with a sample size of 900 reported a reduction of 4 mmol/mol (2.5%) ($p < 0.001$) at a mean follow up period of eight months.[35]

There is discrepancy observed in two of the studies which reported the HbA1c change at one-year follow up. Kramer et al. reported a HbA1c at 57.1 mmol/mol (7.4%) with a baseline of 57.6 mmol/mol (7.4%) ($p = 0.688$).[32] On the other hand, Paris et al. noted a decrease in HbA1c to 62.8 mmol/mol (7.9%) with a baseline of 69.4 mmol/mol (8.5%) which was reported to be statistically significant ($p < 0.05$).[30] Interestingly, the subgroup analysis of both studies showed a statistically significant increase in HbA1c in well-controlled participants with a baseline HbA1c of <58 mmol/mol (7.5%) ($p < 0.05$) and a reduction in HbA1c in less-controlled participants with a baseline HbA1c of >58 mmol/mol (7.5%) ($p < 0.001$).[30,32] These findings were consistent with the IMPACT trial which only included individuals with close-to-target baseline HbA1c defined as <58 mmol/mol (7.5%).[24] Paris et al. described that patients with poorly controlled diabetes improved their disease management due to self-confidence in using FGM.[30] This is further supported by the subgroup analysis reported in a few other observational studies which consistently demonstrated a significant reduction in HbA1c in FGM users with baseline HbA1c of >58 mmol/mol (7.5%).[30,32,33,35,37]

In summary, the reduction in HbA1c after use of FGM is evidently demonstrated in many studies. It is possible that patients with a suboptimal HbA1c will benefit more from the use of FGM in order to achieve better glycaemic control as compared to already well-empowered and motivated individuals with well-controlled diabetes. This novel technology which is easy to operate and able to minimise the psychological effect of finger prick test could potentially be the main factor in improving poor adherence of SMBG and subsequently achieving better glycaemic control in those with poor control at baseline.

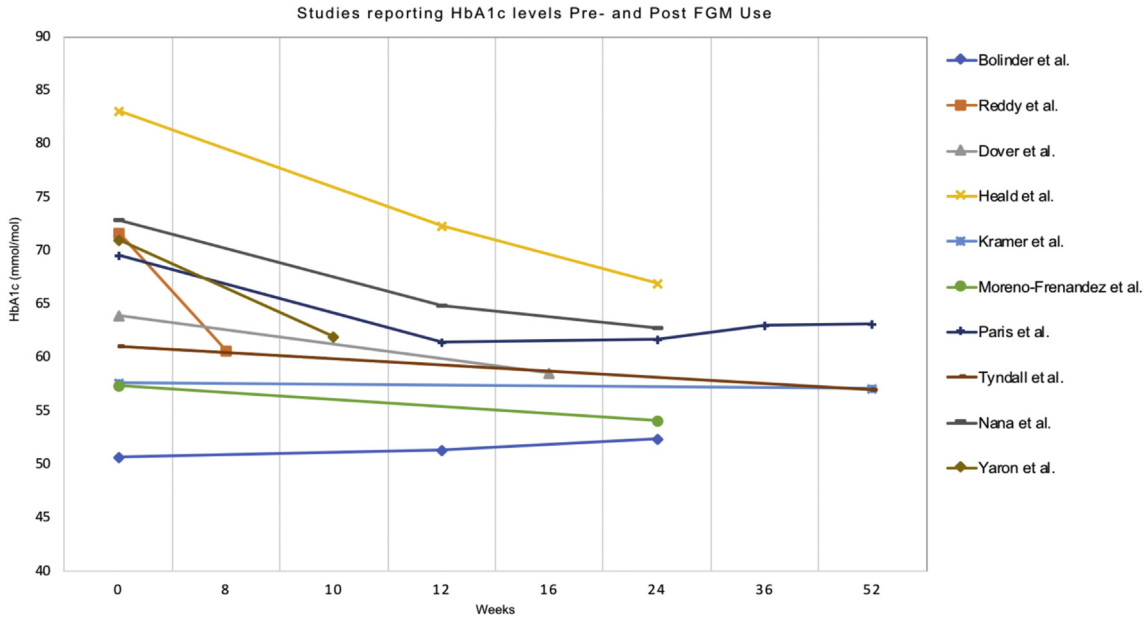

Fig. 2. Studies reporting HbA1c levels pre- and post-FGM use. Studies which did not provide post-FGM HbA1c, specify the time period between pre- and post-FGM or only described change in HbA1c without a baseline HbA1c value are not included.

6. Glycaemic variability

6.1. Time spent in hypo- and hyperglycaemia

The built-in AGP feature FGM provides a simple way for users to visualise the glycaemic variability. It also records hypoglycaemic events when the interstitial glucose level is lower than 3.9 mmol/L for a duration >15 min. Eight studies have reported time spent in hypoglycaemia with inconsistency in interpretation of this outcome.[24–27,30,32,33,37] In terms of time spent in hypoglycaemia in 24 h, two RCTs reported significant reduction in time in hypoglycaemia at 6 and 12 months.[24,25] In terms of episodes of hypoglycaemia, Yaron et al. showed no significant difference between intervention and control groups, Dover et al. reported five less episodes of hypoglycaemia over the course of two weeks, Nana et al. reported a change of −3.2 ($p < 0.001$) events in a day while Paris et al. demonstrated an increase of six episodes of hypoglycaemia in a month ($p < 0.001$).[27,30,33,37] On the other hand, only three RCTs reported on time spent in hyperglycaemia. Bolinder et al. described a reduction in time spent in hyperglycaemia from 1.85 h to 1.67 h per day ($p = 0.0247$).[24] The remaining two studies noted no statistical change to time spent in hyperglycaemia at both two months and one-year periods.[25,26] Overall, most studies showed a statistically significant reduction of time spent in hypoglycaemia after the use of FGM while the change in time spent in hyperglycaemia was clinically insignificant.

6.2. Time in range

The time in target section on the reader provides a summary of percentage time in range as well as above or below target for various periods of time which is helpful in identifying variability of glucose level and tailoring management promptly. The intervention arm in the IMPACT trial showed a significant improvement in time in target, from 15.0 ± 2.5 h to 15.8 ± 2.9 h ($p = 0.0006$) in those using FGM. However, the generalisability of this result is limited by the inclusion of only patients with a baseline HbA1c of <58 mmol/mol.[24] The REPLACE study only showed 0.1 ± 4.4 h ($p = 0.8519$) change at 12 months.[25] Similarly, Reddy et al. which made a head-to-head comparison between FGM and CGM described an improvement in percentage time spent in glucose target with a median change of 5.3% and 12.7% respectively.[26]

7. Frequency of SMBG

The reliable accuracy of FGM delivers assurance and confidence to the users in reducing the number of finger prick tests which often cause distress and inconvenience in patients with diabetes.[23] All studies found that the frequency of SMBG had significantly reduced after initiation of FGM. Kramer et al. demonstrated a reduction in number of SMBG performed to an average of less than once a day which was comparable to the findings in the IMAPCT and REPLACE studies.[24,25,29] The recent change in the UK Driver and Vehicle Licensing Agency (DVLA) guideline allowing road users with diabetes to check their blood glucose level prior to starting journey or during breaks using FGM is set to further reduce SMBG frequency.[59]

8. Quality of Life (QoL) and patient reported outcome measures (PROMs)

QoL and PROMs evaluated in the included studies are summarised in Table 1. The assessment tools used in reporting QoL or PROMs across studies are heterogeneous. Two RCTs by Bolinder et al. and Yaron et al. showed no significant improvement in Diabetes Quality of Life (DQoL) and Audit of Diabetes Dependent Quality of Life (ADDQoL) scores respectively.[24,27] It should be noted that 87.5% of the intervention group in the study conducted by Yaron et al. stated that they were very satisfied with the use of the technology. Moreover, the intervention group found the use of FGM to be significantly more flexible than SMBG ($p = 0.019$) and would recommend the technology to the control group ($p = 0.023$). Yaron et al. also discussed high overall satisfaction in both control and intervention groups and hypothesised that the intensive and regular follow-ups in their study has improved the treatment satisfaction in both groups and masked the effect of FGM in terms of satisfaction in the intervention group.[27] On the contrary, Haak et al. which only had two outpatient clinic follow-ups during the six-month study period showed a significant improvement in Diabetes Treatment Satisfaction Questionnaire (DTSQ) score ($p < 0.0001$).[60]

Other observational studies reported significant improvement in Diabetes Distress Scale (DDS) as well as World Health Organisation well-being index (WHO-5) after FGM use.[28,33,37] The WHO-5 questionnaire is a widely used tool to assess subjective psychological well-being in diabetes and can be used as a well validated depression screening tool in diabetes.[61–64] Indeed, the significant improvement in WHO-5 scores demonstrated in the Japanese study may reflect the possibility of risk reduction in having depression in patients with diabetes. The subgroup analysis of Mitsuishi et al. who focused on the use of FGM regarding mental health and patient satisfaction found that patients with T1DM have a better WHO-5 and DTSQ score.[28] On the other hand, the validated DTSQ was used in all studies reporting treatment satisfaction. Two prospective studies observed improved DTSQ scores in FGM users which supported the findings in the IMPACT trial.[24,27,28,32]

A study published by Overend et al. in 2019 on qualitative analysis in the form of semi-structured interview reported positive feedback from the patients. One of the key aspects discussed was QoL and improved wellbeing in which most patients reflected the cultivation of self-care and diabetes management. The users reported the convenience and benefit of involvement of family or carers in the use of the device when the individual was unwell or driving. Increased empowerment confidence in disease management as well improvements in self-esteem have also been associated with FGM use.[34] Overall, despite the heterogeneity in reporting tools and methods on QoL and PROMs, the positive impact of FGM on patients' QoL and treatment satisfaction remains substantially evident.

9. Adverse events related to device use

FGM device-related adverse outcomes have been reported in several studies with the main concerns being sensor wear reaction as well as sensor site insertion symptoms. The primary side effects with regards to sensor wear are erythema, rash and itching; these were reported to have contributed to 87% ($n = 117$) of the total adverse events in the REPLACE study and 67% ($n = 167$) in the IMPACT study.[24,25] These findings remained consistent in the clinical setting with four recent observation studies reporting the aforementioned symptoms.[28,31,32] Of note, most reactions were mild in nature and required no medical intervention. Bolinder et al. have also detailed sensor site insertion symptoms such as pain ($n = 38$), bleeding ($n = 25$), oedema ($n = 8$), induration ($n = 5$) and bruising ($n = 5$).[24] In the two multicentre RCTs, ten patients had to withdraw due to complications from the use of device.[24,25] It is not uncommon for patients to develop allergy-like reaction to medical adhesives especially with the prolong wear of FGM or CGM in combination with the chronicity of device use and limited sites for attachment.[65] A study has described the chemical compound, isobornyl acrylate found in FreeStyle Libre can sensitise the skin and potentially precipitate allergic contact dermatitis. 12/15 patients developed intense pruritus at the application site after more than two weeks of FGM wear.[66] Bolinder et al. have reported use of topical cream and oral medications in treating allergic reaction at sensor site.[24] Although there is no guideline on managing side effects of FGM attachment site, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom have advised against the use of topical treatment on sensor application site as this may interfere with device performance and subsequently affect the insulin dosing and carbohydrate intake

according to the false reading.[67] In summary, sensor site adverse reactions can be detrimental to a patient's engagement with the device and healthcare professionals should be aware of the supplementary products available to help with FGM adhesives, taking into considerations of different variables such as climates, daily activities and patient's choice.

10. Risk of acute and severe complications

While tight glycaemic control can reduce long term diabetes complications, it can also increase the risk of hypoglycaemia as periods of hyperglycaemia are avoided at all costs. Risk of severe hypoglycaemia, defined as hypoglycaemic episodes requiring third part assistance, can be detrimental and have been associated with significant cardiac and cerebrovascular events.[68] To date, the literature has not revealed an association of increased frequency of severe hypoglycaemia with FGM in T1DM and insulin-dependent T2DM.[29,30,35]

On the contrary, persistently raised glucose level can lead to potentially dangerous consequences including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS). Evidence of the effect of FGM in reducing incidence of DKA or HHS has been sparse. Large RCTs with follow-up up to one year did not observe any episodes of DKA or HHS.[24,25] Tyndall et al. showed a significant reduction in hospital admission for DKA after commencement of FGM ($p = 0.043$).[35] The trend arrow information in FGM that demonstrates direction of glucose reading fluctuation in the last 15 min provides invaluable therapeutic guidance and allows timely intervention in preventing acute complications.[69] All in all, patient education on the utilisation of trend arrow information and regular scanning with FGM will be useful in overcoming glucose excursions and minimising risks of complications such as severe hypoglycaemia, DKA and HHS. As the incidence of these serious complications remains high, further studies with larger cohort or longer study duration are warranted to validate the benefits of FGM on prevention of DKA or HHS.

11. Conclusion

Although yet to be assessed in the context of non-insulin using T2DM patients, the emergence of FGM as an innovative technology has transformed diabetes care and had a positive impact on psychological wellbeing in patients with diabetes. FGM, as a hybrid of CGM and SMBG, is able to overcome SMBG's limitation in glycaemic variability detection and serve as a more affordable alternative to CGM without the need for calibration.

Further studies have provided addition evidence to support their use and give confidence to practitioners who manage patients with diabetes. The studies have further validated the beneficial effects of FGM on clinical outcomes in diabetes, notably the marked improvement in HbA1c. It is also confirmed that the consistent use of FGM can greatly improve patient's QoL and treatment satisfaction. This ultimately enhances patient compliance and ensures better glycaemic control. By generating AGP, FGM can inform diabetes management decision made by clinicians. Evaluation of QoL and PROMs will require a standardised approach to allow comparability of the results and evidence.

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CRediT authorship contribution statement

Eshen Ang: Methodology, Formal analysis, Validation, Investigation, Writing - original draft, Visualization.**Zong Xuan Lee:**Methodology, Formal analysis, Validation, Investigation, Writing - original draft, Visualization.**Sacha Moore:**Conceptualization, Validation, Methodology, Writing - review & editing, Supervision.**Melanie Nana:**Conceptualization, Validation, Methodology, Writing - review & editing, Supervision.

Declaration of competing interest

None.

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