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RESEARCH ARTICLE

Clinical insights from continuous glucose monitor use in patients living with type 1 diabetes in rural Malawi

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Background: People living with type 1 diabetes (PLWT1D) in low-resource settings face numerous barriers to achieving glycaemic targets. Use of continuous glucose monitoring (CGM) is increasing but uptake remains low in sub-Saharan Africa. In 2022, a randomised controlled trial (RCT) evaluating feasibility of CGM was conducted in Neno, Malawi. This is a retrospective sub-study examining three-month blood glucose trends from participants randomised to the CGM arm.
Methods: This is a sub-study of a 2:1 parallel arm open randomised controlled trial to assess the feasibility and impact of CGM. Ambulatory glucose profiles (AGP) from 29 participants in the CGM arm were reviewed by clinicians. Two patient reports with AGP patterns exemplifying observed trends were identified and described in detail, and interventions were highlighted.
Results: Time below optimal blood glucose range was highest from 12 am to 6 am: 7.0%, 6.9%, and 5.1% for months one, two, and three respectively. From baseline to endline, the average absolute value (increase or decrease) of the percentage change in total daily dose (TDD) of insulin was 11.2%. Case studies of two patients who demonstrated a positive impact of CGM are reported.
Conclusions: CGM provided compelling insights into blood glucose trends with significant clinical implications, specifically high prevalence of overnight hypoglycaemia. The ability to monitor blood glucose levels is critical because high variability and severe hypoglycaemia increase the risk of morbidity and mortality. CGM is a tool that can enhance patient education and the ability to guide treatment decisions for patients and clinicians in low-resource settings.

Keywords: blood glucose patterns, continuous glucose monitoring (CGM), sub-Saharan Africa, type 1 diabetes (T1D)

Introduction

Type 1 diabetes (T1D) is a chronic illness characterised by the body's inability to produce insulin due to autoimmune destruction of beta cells in the pancreas. An estimated 8.4 million individuals live with T1D worldwide; of those one-fifth (1.8 million) live in low- and lower-middle income countries (LLMICs).[1] Life expectancy of a 10-year-old diagnosed with T1D ranges from a mean of 13 years in low-income to 65 years in high-income countries.[2]

People living with T1D (PLWT1D) in Africa, especially in rural areas, are more likely to have suboptimal glycaemic control and frequent hospitalisations due to diabetes-related complications, such as diabetic ketoacidosis (DKA) and severe hypoglycaemia.[3–6] In LLMICs, access to T1D care is limited, with low availability and high cost of insulin and other supplies and diagnostics, lack of T1D knowledge, and absence of readily accessible guidelines.[7,8] In Malawi, the frequency of DKA and severe hypoglycaemia is high, and mean HbA1c among children ages 5–19 receiving care at a hospital outpatient clinic was 13.2%.[9] While self-monitoring of blood glucose (SMBG) is accepted as standard of care, it is often unavailable.[9,10]

SMBG is a cornerstone of diabetes self-management. Despite inclusion in global guidelines, access to and use of glucose meters in LLMICs remains limited, though recent studies have shown that SMBG is feasible and can decrease HbA1c in these settings.[11–15] In high-income countries (HICs), continuous glucose monitoring (CGM) is increasingly being considered as the standard of care for PLWT1D and has been shown to significantly improve HbA1c and time in range (TIR) while decreasing the risk of severe hypoglycaemia.[16] Benefits for the wearer include reduced use of fingersticks, reductions in glycaemic variability, high or low blood glucose alarms, real-time feedback of blood glucose levels, and an improved sense of mental well-being.[17,18] CGM can also provide valuable information to providers to improve patient education, make individualised treatment decisions, and improve patient engagement.[19] TIR derived from CGM data is increasingly accepted as the standard measure of diabetes care due to the ability to understand variability in addition to a mean.[20]

Despite strong evidence for efficacy and effectiveness of CGM in HICs, adoption and research in LLMICs has been limited. While cost is a primary barrier, additional concerns can include patient literacy, numeracy, technological literacy, and access to device charging. An RCT in India evaluating blinded CGM plus SMBG compared with SMBG found minimal change in HbA1c, but a statistically significant decrease in total daily

dose (TDD) of insulin in the intervention arm.[21] A feasibility trial in Uganda and Kenya found two-week wearing of a blinded CGM to be feasible, and noted low TIR (30 +/- 19%) and frequent hypoglycaemia (7% of time spent at less than 55 mg/dL).[22] Several studies found that retrospective review of CGM data was useful to clinicians in providing clinical insights to guide patient education and medication adjustment.[21–23]

In 2022, a three-month study evaluating the feasibility of CGM in PLWT1D in Neno, Malawi showed that CGM, while not without its challenges, was feasible and acceptable.[24,25] In this paper we present a retrospective analysis of individuals' CGM and insulin regimen data to understand factors that may be affecting glucose patterns. This study is approved by the National Health Sciences Research Committee of Malawi (IRB Number IR800003905) and Mass General Brigham (IRB number 2019P003554). The clinics where the study was conducted also hold an umbrella IRB for regularly collected clinic data with the National Health Sciences Research Committee of Malawi (IRB number 20/10/1216).

The objectives of this study were to:

1. Identify clinical trends and blood glucose patterns illuminated through CGM.
2. Describe how CGM use impacted patient education and change in treatment regimens.

Methods

Setting

This study was conducted in two rural hospitals in Neno, Malawi. In 2018, Partners In Health, in partnership with the Ministry of Health in Malawi, started implementing Package of Essential Interventions for Noncommunicable Disease Plus (PEN-Plus) clinics to decentralise care for severe non-communicable diseases (NCDs) at two centres.[26] PEN-Plus trains mid-level providers including nurses and clinical officers to care for patients with complex severe NCDs including T1D, rheumatic heart disease, and sickle cell disease.[27–29] PLWT1D typically attend consultations monthly to receive refills of insulin and other diabetes supplies. Since 2019, the clinics have provided glucose meters and enough test strips to check once daily.[15] PLWT1D typically use intermediate-acting human insulin (NPH) twice daily (BID) and fast-acting (regular) two to three times daily (TID).

Study design and participants

This report is a sub-study conducted retrospectively after a 3-month feasibility 2:1 parallel arm open randomised controlled study. Methods for the original trial have been previously published.[24,25] All patients receiving care in Neno with a clinical diagnosis of T1D in any age group with diabetes duration of at least one year were invited to participate in the study. Exclusion criteria included pregnancy, mental impairment, or inability of the participant or care provider to use a CGM device.

Participants in the CGM arm of the study were provided with a transmitter, receiver, disposable sensors (Dexcom G6, Dexcom, San Diego, CA, USA) for three months of wear, and a solar charger. Participants received training on the features of CGM including alarms and arrow interpretation. Participants were trained to change sensors on their own, or were advised to follow up after 10 days for new sensor insertion by study staff.

Data sources

Dexcom clarity reports

A team of clinical mentors and providers who administered the study identified trends and clinical patterns through results obtained in Dexcom Clarity software (https://clarity.dexcom.eu/). Anonymous baseline 14-day, endline 14-day, and endline 90-day Dexcom Clarity reports including overview, daily patterns, and Ambulatory Glucose Profile (AGP) were exported for all patients in the intervention arm of the study.

Regularly collected clinical data

Study staff retrospectively reviewed routinely collected clinical data from paper-based documentation. Participant weight, insulin doses, and any education completed were extracted from these records.

Outcomes and analysis

Initial analysis focused on identification of previously unidentified blood glucose trends in PLWT1D in this setting. We then describe how CGM use impacted diabetes treatment decisions. Case studies exemplifying these trends are described in detail. All data analysis was completed in STATA version 15.1 (StataCorp LLC, College Station, TX,. USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Specific outcomes and analysis include the following.

Temporal trends in time in range

Time in range (TIR) was defined using the standard range of blood glucose between 70 mg/dL and180 mg/dL.[20,30] Out of range glucose levels were labelled as very high (> 250 mg/dL), high (181 mg/dL–250 mg/dL), low (54 mg/dL–69 mg/dL), and very low (< 54 mg/dL). Values were calculated through export of the Clarity datasets, which contained every recording registered by the CGM devices. Participants did experience periods without observations recorded, which we included by considering five-minute periods with no observations as a 'missing' observation (about 36% of total observations). Most of these missing observations (about 73%) were due to the need for sensor replacement; participants typically visited the clinic for replacement at 2-week intervals, but sensors lasted 10 days.[24] Data were stratified by month (one to three) and time of day (12 am–6 am, 6 am–12 pm, 12 pm–6 pm, 6 pm–12 am). We summarised each individual's blood glucose measures by calculating the proportion of time the sensor was active in each of the ranges already specified. We report these proportions in each range of blood glucose values averaged across the study participants.

Changes in insulin doses

We used baseline and endline weight-based total daily dose of insulin (TDD) to evaluate changes in insulin doses over the course of the study. To account for both increases and decreases in TDD, absolute percentage change in TDD from baseline to endline was calculated to avoid positive and negative changes averaging out to zero.

Interventions initiated by CGM use

Education, counselling, and changes to treatment regimen based on CGM trends were tracked throughout the study. We identified common education themes and the number of times education or counselling related to each theme was performed. Additionally, the number of times insulin doses were increased or decreased was tabulated.

Case studies

Clinical mentors (two nurse practitioners and one physician specialised in T1D care) and clinicians (one clinical officer and one specialty trained nurse) sequentially reviewed reports for all patients. Two case studies were identified of study participants who exemplified previously unforeseen clinical trends, benefits from use of technology, and challenges associated with CGM use.

Results

Demographics

A total of 29 participants were assigned to the CGM arm. Demographics and results of the primary study are explained in detail in a previous paper.[24,31] Here we report results specific to a retrospective analysis of participants in the CGM arm only. Of the participants in the CGM arm, 14 were female and 15 were male. Mean age was 31.1 years (range 8–51), and mean diabetes duration was 6.1 years (range 1–24). Mean body mass index (BMI) was 21.4 (standard deviation [SD] 3.6). Point of care (POC) HbA1c at baseline was 8.5% (SD 2.2) and 7.4% (SD 1.9) at endline (Table 1).

Temporal trends in time in range

Time below, in, and above range was stratified by month and time of day (Figure 1) for all 27 participants who wore the CGM for more than 1 week. TIR was highest from 12 am to 6 am: 35.0%, 45.7%, and 44.4% for months one, two, and three respectively. Time below range was also highest from 12 am to 6 am: 7.0%, 6.9%, and 5.1% for months one, two, and three respectively. Time above range was highest from 6 pm to 12 am: 71.7%, 69.9%, 66.8% for months one, two, and three respectively (Table 2).

Changes in insulin doses

At baseline, 27 participants in the CGM arm were on an insulin regimen of NPH BID and regular BID, while 2 participants were on a regimen of NPH BID and regular TID. At endline, 28 participants were on an insulin regimen NPH BID and regular BID, while 1 participant was on a regimen of NPH BID and regular TID. From baseline to endline, the average absolute percentage change in TDD was 11.2% (Table 1). Mean weight-based TDD was 1.02 u/kg/day (SD 0.47) at baseline and 1.04 u/kg/day (SD 0.48) at endline. In the usual care arm, only two insulin adjustments were made.

Table 1: Demographic data of participants, change in HbA1c and change in insulin doses

Location (% Upper Neno)	48.0
Age (years), mean (range)	30.9 (8, 51)
Sex, *n* (%)	
Female	14 (48.0%)
Male	15 (52.0%)
Diabetes duration (years), mean (range)	6.1 (1, 24)
BMI ages 21–51, mean(SD), $n = 23$	22.4 (3.0)
BMI z-score ages 8–20, mean(SD), $n = 6$	−0.968 (2.2)
HbA1c, mean (SD)	
Baseline	8.5 (2.2)
Endline	7.4 (1.9)
Weight based total daily dose (units/kg/day), mean (SD)	
Baseline	1.02 (0.47)
Endline	1.04 (0.48)
Absolute percentage change in total daily dose, % (range)	11.2 (0, 45.5)

Data are given as *n* (%), mean, SD, or range.

Interventions initiated by CGM use

Education and counselling were conducted 68 times, while insulin was decreased 13 times and increased 15 times (Figure 2). The two most frequent education topics were diet and timing of insulin doses, followed by insulin injection technique, use of glucose meter when CGM not working, and identification and treatment of hypoglycaemia (Figure 2).

Case studies

Two patients were identified whose AGP patterns exemplified observed trends. Patient A is a 9-year-old boy in 4th grade living with T1D for 4 years with a BMI of 17.7 kg/m^{2,}. He lives with his father, who works as a labourer, and his mother, who is a homemaker. They travel 25 km by motorcycle taxi to get to clinic, which typically takes two hours one way. His mother is the primary caretaker, accompanying him to visits, giving him insulin, and preparing food. At baseline, Patient A was taking NPH 10 units am, 4 units pm and regular 4 units am, 6 units pm, a TDD of 24 units, or 0.8 u/kg/day. At the first visit after CGM was placed, significant nocturnal hypoglycaemia was noted, with 19.2% low including 7.5% very low (Figure 3). The mother noted that the patient often felt lethargic and weak in the morning, but providers and the family were previously unaware that he was having nocturnal hypoglycaemia. The family was educated on signs and symptoms of hypoglycaemia, as well as giving a snack prior to bed, and evening regular was reduced to 2 units (66% decrease). Hypoglycaemia persisted at the next visit, and insulin was further reduced to NPH 10 units am, 2 units pm (50% decrease) and regular 4 units am 2 units pm. By endline, Patient A was taking NPH 10 units am, 2 units pm and regular 4 units am only, with a TDD 16 units, or 0.53 u/kg/day (33% decrease). A change of −11.4% of time spent in low range was noted from baseline to endline, and time in very low range decreased from 7.5% to 4.6% (Figure 3). While TIR decreased (33.5% to 22%), the reduction in coefficient of variation (CoV) from 62.9 to 46.8 and the improvement in time below range represents a substantially decreased risk of morbidity or mortality from hypoglycaemia.

Patient B is a 34-year-old female living with T1D for 4 years, with a BMI of 26.4 kg/m^2. She completed high school education, is married, lives with one child, and is employed at a salon. She travels 12 km by motorcycle taxi to get to clinic, which typically takes one hour one way. At baseline, Patient B was taking NPH 28 units am, 18 units pm and regular 5 units TID, with a TDD of 61 units, or 0.95 u/kg/day. At baseline, TIR was 9.5%, with time above range 90.5% and a CoV of 27.1 (Figure 3). Prior to the study, patient B was resistant to making insulin adjustments due to fear of hypoglycaemia. CGM allowed the patient to feel comfortable increasing insulin doses. Based on the hyperglycaemia trends illuminated by CGM, clinicians first confirmed that Patient B was taking the correct doses, at the correct time, and rotating injection sites. They then provided her with additional education on portion size, injection technique, and increasing exercise. By endline, Patient B was taking NPH 40 units am, 26 units pm and regular 8 units am and lunchtime, 10 units pm, with TDD 92 units, or 1.31 u/kg/day (50% increase). TIR had improved significantly to 70.4%, with a very small increase in time below range (0% to 0.6%) and a stable CoV of 30.8 (Figure 3).

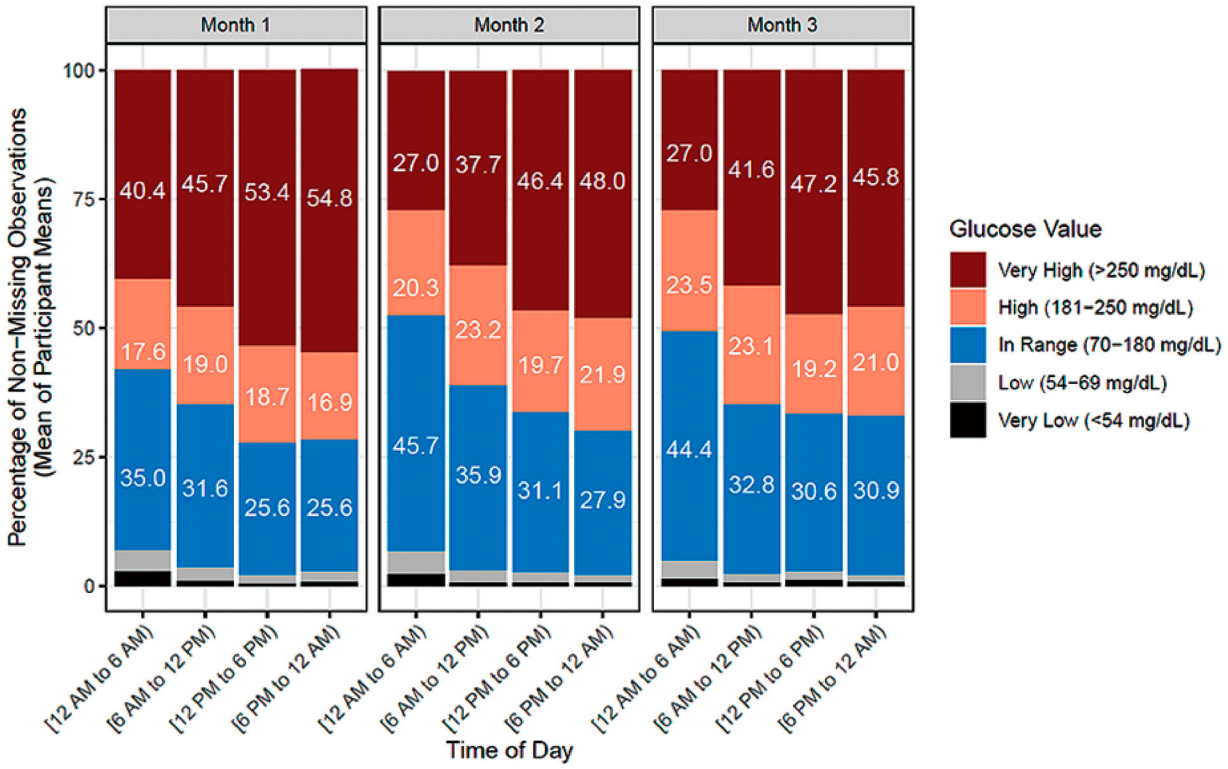

Figure 1: Average proportion of blood glucose values in different ranges by month and time of day.

Table 2: Average glucose, proportion of observations in blood glucose ranges, and proportion of time sensor was active by month and time of day

Month	Time of day	Average glucose (mg/dL)	Very low (< 54 mg/dL), %	Low (54–69 mg/dL), %	In range (70–180 mg/dL), %	High (181–250 mg/dL), %	Very high (> 250 mg/dL), %	Sensor active, %
1	(12 am to 6 am)	221.4	3.0	4.0	35.0	17.6	40.4	62.8
1	(6 am to 12 pm)	243.4	1.2	2.5	31.6	19.0	45.7	61.6
1	(12 pm to 6 pm)	266.5	0.6	1.7	25.6	18.7	53.4	64.1
1	(6 pm to 12 am)	265.1	1.0	1.9	25.6	16.9	54.8	64.4
2	(12 am to 6 am)	195.2	2.5	4.4	45.7	20.3	27.0	64.4
2	(6 am to 12 pm)	225.8	0.8	2.3	35.9	23.2	37.7	62.8
2	(12 pm to 6 pm)	247.1	0.8	2.0	31.1	19.7	46.4	64.4
2	(6 pm to 12 am)	252.3	0.7	1.6	27.9	21.9	48.0	64.9
3	(12 am to 6 am)	197.4	1.5	3.6	44.4	23.5	27.0	58.3
3	(6 am to 12 pm)	236.7	0.8	1.7	32.8	23.1	41.6	56.4
3	(12 pm to 6 pm)	249.5	1.3	1.7	30.6	19.2	47.2	61.8
3	(6 pm to 12 am)	247.9	1.0	1.3	30.9	21.0	45.8	60.4
1	All day	248.7	1.4	2.5	29.6	18.1	48.4	63.2
2	All day	230.4	1.2	2.6	35.1	21.2	39.8	64.1
3	All day	235.2	1.2	1.9	33.4	22.6	40.9	58.8

Glucose numbers reported are percentages of time sensor was active in very low, low, in range, high, and very high ranges stratified by time of day and month.

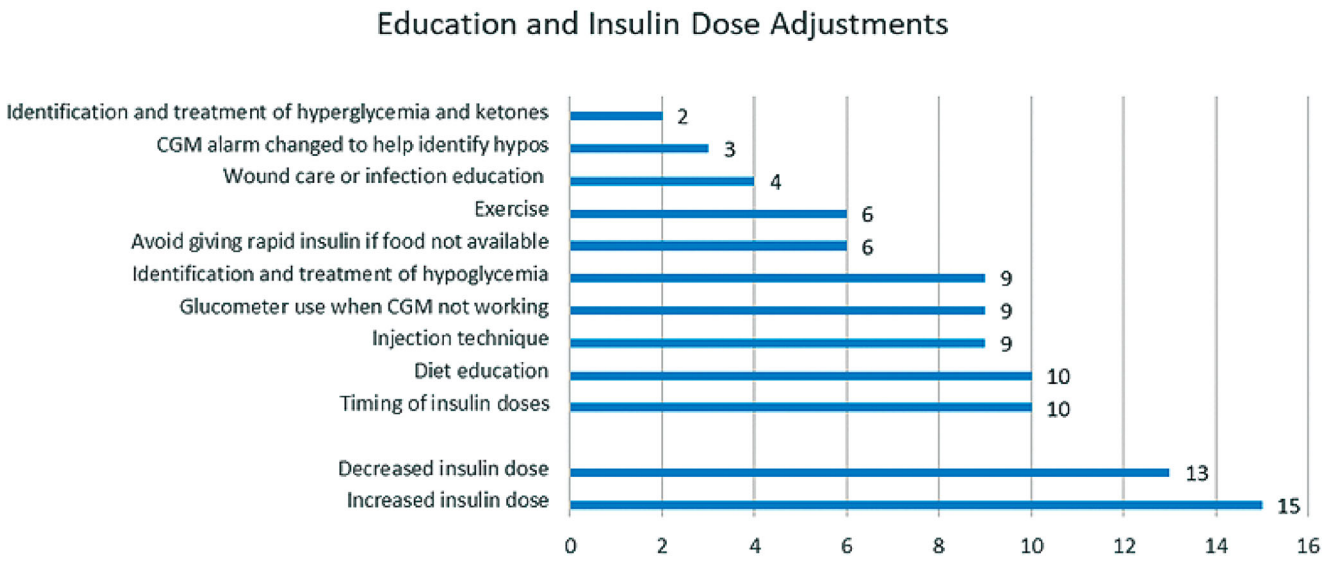

Figure 2: Number of times education was given, or insulin adjusted by education type.

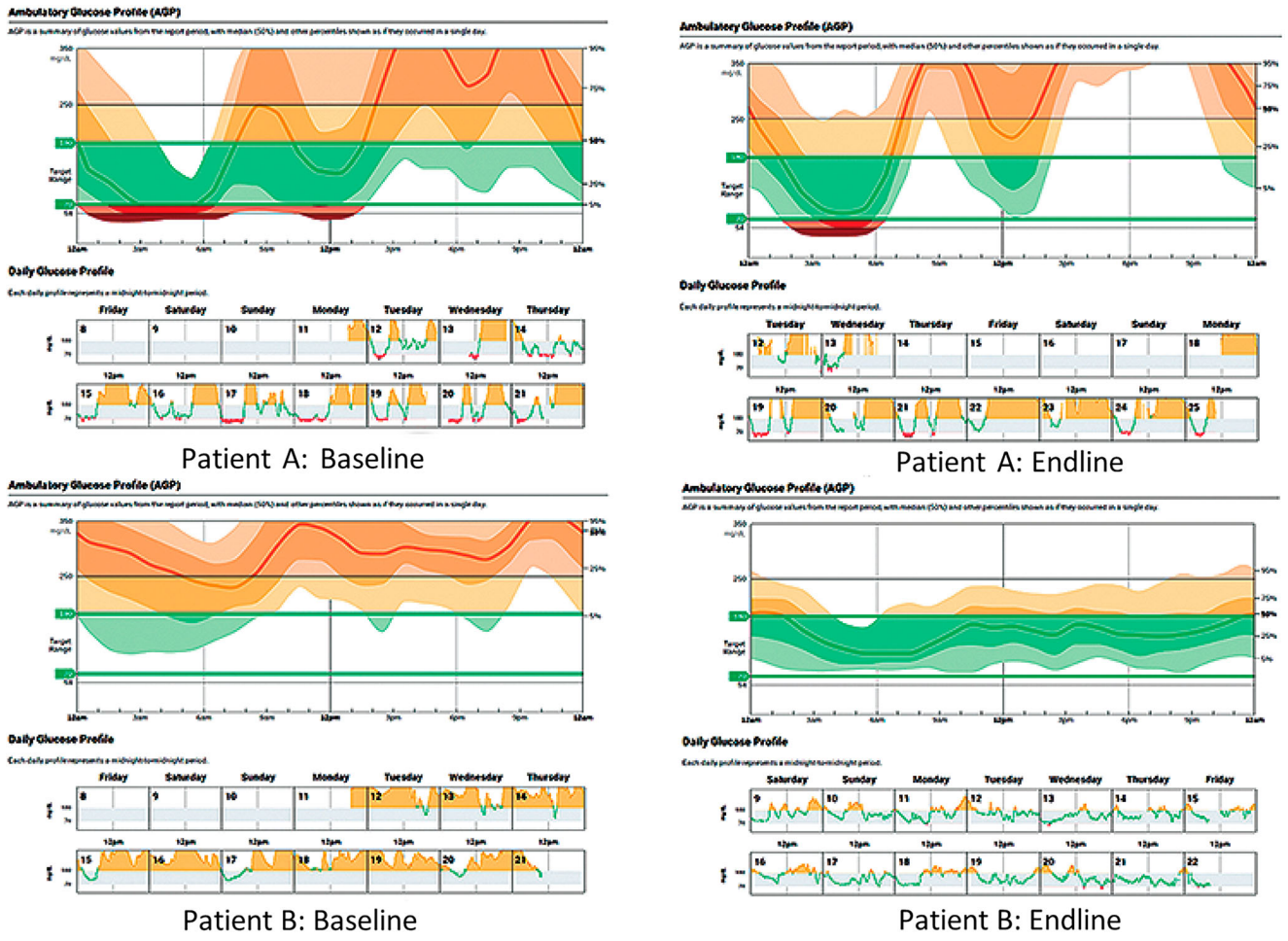

Figure 3: Ambulatory glucose profile and daily glucose profile of patients (A and B) at baseline and endline.

Discussion

This is a retrospective sub-study from a three-month randomised controlled trial to assess feasibility and clinical outcomes of introducing CGM in two rural hospitals in Neno, Malawi. The most compelling findings included TIR well below target, high variability of blood glucose values, and high prevalence of overnight hypoglycaemia. TIR at all time points increased by 3.9% from month one to month three, while time below range decreased by 0.8%. Change in time in range over time was more pronounced when looking at data stratified by time

of day. Though this change was small and the study was not powered to detect clinically significant change in TIR, it may represent a positive impact of CGM on improving TIR and decreasing time below range. While participants were not taught to make insulin adjustments based on sensor values, they were taught to interpret alerts and alarms, to utilise CGM to predict and treat hypoglycaemia, and to contact providers in the case of prolonged hyperglycaemia.[25]

Time above range was at least 2.5 times the global targets of 25% during all months, which over time leads to significant risk of diabetes-related complications.[20,30] Food insecurity and seasonal variability in food access may have affected the high rates of hyperglycaemia and glucose variability. Time below range exceeded global targets of 4% less than 60 mg/dL and 1% less than 54 mg/dL during the 12 am to 6 am time period during all months. While there are minimal epidemiologic data on mortality due to hypoglycaemia in PLWT1D in low-resource settings, our findings are in congruence with the high prevalence of hypoglycaemia seen in studies of PLWT1D in Ethiopia, Uganda, and Kenya,[22,32] while adding clarity that the majority of hypoglycaemia is occurring nocturnally. Nocturnal hypoglycaemia is particularly concerning due to decreased ability of the patients to feel symptoms while sleeping, leading to increased risk of hypoglycaemia unawareness, seizures, or death.[33,34] The majority of cases of nocturnal hypoglycaemia were previously unknown to providers, and providers found CGM empowered them to address this through addressing food insecurity, education gaps, and adjusting insulin regimens.

Insulin regimens were increased and decreased at roughly the same frequency. Though weight-based TDD had no significant change, this may have been because some doses were increased, while others were decreased. Average absolute percentage change in TDD was 11.2%, which aligns with standards of care that suggest adjusting insulin regimens by 10–20% in response to blood glucose patterns.[35,36] Both case studies required insulin dose changes of closer to 50%, showing how CGM allowed providers to be aggressive in making insulin dose adjustments.

Further research is warranted to evaluate whether the benefits of CGM can be enhanced with structured diabetes self-management education, use of long-acting insulin analogues, or both. CGM can be used not only to inform treatment decisions but also to individualise patient education on factors contributing to hypo- and hyperglycaemia, symptom awareness, blood glucose pattern recognition, and when to contact the diabetes management team. In HICs, long-acting insulin analogues are the standard of care because they do not peak, improve HbA1c, and decrease hypoglycaemia.[37,38] Despite these documented benefits, guidelines continue to recommend intermediate-acting insulin in low-resource settings, primarily due to a lack of evidence for cost-effectiveness.[12,39] We encourage use of CGM in any future research in this area, given the ability to detect change in nocturnal hypoglycaemia specifically.

This study had several limitations. As a retrospective and observational sub-study, we should be wary of causal overinterpretation. Further, the PEN-Plus clinic in Neno has been operating with support from Partners In Health since its inception in 2018.[26] Baseline HbA1c was 8.5%, which is significantly lower than at other clinics in the region.[3,9,40] It is unclear whether this is a reflection of better glycaemic control among patients in Neno as a result of additional resources, inaccurate point-of-care HbA1c tests, or population factors such as hemoglobinopathies. However, these results are consistent with previous research in Neno.[15] Different access to resources from other clinics in the region may limit generalisability. However, the critical findings from this study, including high prevalence of nocturnal hypoglycaemia and high variability in blood glucose, are consistent with other studies in sub-Saharan Africa (SSA).[22] These findings are supported by length of sensor wear, which was a major strength of the study. Previous studies in SSA have evaluated blood glucose trends from a single two-week sensor, typically a flash glucose monitor that requires scanning by the wearer to record glucose values.[21–23] Three months of sensor wear allowed for providers to develop competency in interpreting sensor data and to see the impact of adjustments to patient regimens.

Conclusions

The importance of availability of a way to monitor blood glucose, whether SMBG or CGM, cannot be understated. The high variability of blood glucose patterns identified during the study reinforced the importance of assessing for and addressing gaps in diabetes education. CGM allowed providers to visualise the impact of patient education and insulin adjustments on blood glucose patterns. However, CGM is not required to assess for dangerous blood glucose patterns or gaps in education. Assessing for nocturnal hypoglycaemia, either with SMBG or review of symptoms, should be an integral part of management for PLWT1D.

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