Continuous Glycemic Monitoring Metrics of Children and Adolescents with Type 1 Diabetes During the Iron Swords War

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ABSTRACT

Background: The Iron Swords war created stressful circumstances that could negatively impact glycemic control in individuals with type 1 diabetes (T1D).

Objectives: To evaluate changes in continuous glucose monitoring (CGM) metrics in pediatric T1D patients during the war.

Methods: This retrospective study included T1D patients monitored by CGM. Metrics from three selected 2-week periods were compared (before the war, after the war outbreak, and 4 months later). Study variables included time-in-range (70–180 mg/dl; 3.9–10 mmol/L), time-in-tight-range (70–140 mg/dl; 3.9–7.8 mmol/L), time-in-marked-hypoglycemia (< 54 mg/dl; < 3 mmol/liter), and time-in-severe-hyperglycemia (> 250 mg/dl; >13.3 mmol/liter). Patients were treated with either a multiple daily insulin (MDI) regimen or insulin pump, with or without an open-source automated insulin delivery (OS-AID) system.

Results: Data of 99 patients were analyzed (mean age 12.2 ± 4.0 years, mean diabetes duration 4.6 ± 3.9 years, 52.5% males). No significant changes in CGM metrics were observed across the entire cohort at any time point. Patients with higher socioeconomic position (SEP; cluster > 7) had better CGM metrics, with an increase in time-in-tight-range in the lower SEP group and in time-in-severe-hyperglycemia in the higher SEP group (P = 0.003). OS-AID users (n=20) had superior pre-war CGM metrics and maintained stable glycemia during the war, MDI users showed increased time-in-severe-hyperglycemia post-outbreak (P = 0.05).

Conclusions: Throughout the war, children and adolescents with T1D treated with insulin pumps maintained relatively stable glycemic control. Susceptibility to change following the onset of war was influenced by SEP and mode of insulin therapy.

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KEY WORDS: continuous glucose monitoring (CGM), open-source automated insulin delivery (OS-AID), pediatric patients, socioeconomic position (SEP, type 1 diabetes (T1D)

On 7 October 2023, Hamas and other Iranian proxies launched a coordinated attack from the Gaza Strip into southern Israel, killing over 1300 people and kidnapping more than 240 innocent civilians [1]. The war involved thousands of missiles fired at Israel from multiple locations, including Gaza, Iran, Lebanon, Yemen, Syria, and Iraq. The conflict resulted in over 1600 Israeli deaths, tens of thousands of injuries, and the displacement of hundreds of thousands from their homes. This constitutes the deadliest attack on Jews since the Holocaust, causing widespread trauma [1]. Nearly all Israelis endured severe stress from the barrage of over 9500 missiles fired within the first few weeks [2]. In addition, many faced the emotional impact of having family members and friends killed, injured, kidnaped, or displaced from their homes [3].

All parts of the country were affected, often leading to the suspension of routine activities and widespread seeking refuge in shelters. The conflict severely impacted Israel's healthcare system, with major medical centers dedicating resources to treating the large number of wounded soldiers and civilians, significantly restricting elective procedures [4]. The situation required rapid adaptation of healthcare facilities to ensure continuous medical care for patients with chronic conditions, while overcoming the numerous challenges posed by this unprecedented crisis.

Glycemic control in pediatric patients is highly influenced by stressful life circumstances [5]. The war in Israel significantly impacted the lives of children and adolescents, including those with type 1 diabetes (T1D). The disruption caused by the conflict, including constant threat, parental military draft or deployment, and school closures, created exceptional challenges for this vulnerable population [6,7]. The closure of educational institue tions and suspension of leisure activities at the onset of the war disrupted the daily routines of children and adolescents, influencing their diabetes management. Stress associated with war may directly affect blood glucose levels and insulin requirements through hormonal changes and indirectly through alterations in treatment adherence, diet, and exercise [8]. Pre-existing characteristics such as low socioeconomic position (SEP) and decreased adherence to therapy may further deteriorate glycemic control during challenging situations [9].

T1D management necessitates regular monitoring of blood glucose levels. Advancements in continuous glucose monitoring (CGM) systems have profoundly improved accuracy and safety [10]. CGM systems measure interstitial glucose levels every 1–5 minutes by means of enzyme-coated electrodes or fluorescence technology. This constant access to glucose data enables people with diabetes to make real-time treatment adjustments, while stored data facilitates comprehensive analysis by healthcare professionals to optimize glycemic control. The use of advanced technologies, such as CGM and automated insulin delivery (AID) systems, may also offer glycemic control support during stressful situations, such as war-associated crises [11]. Specifically, CGM delivers real-time glucose data, allowing patients and/or parents to manually adjust insulin doses, whether through injections or by pump. Some of the patients who use AID systems benefit from an algorithm that automatically adjusts insulin delivery via an insulin pump based on CGM data, potentially reducing glycemic fluctuations [12]. In this study, we assessed the impact of the Iron Swords war on CGM metrics in children and adolescents with T1D.

PATIENTS AND METHODS

STUDY DESIGN

This single center observational retrospective study of children and adolescents with T1D was based on data collected from electronic medical records and from CGM data using Dexcom Clarity software. More than 70% of patients with T1D at our center use CGM (Dexcom G6 or Medtronic Enlite Sensor; Dexcom, Inc., USA) or a Flash Glucose Monitor (FreeStyle Libre; Abbott, USA). Only those using Dexcom CGM routinely share their glucose data with the clinic, allowing the diabetes care team to access the information directly without requiring any interaction with patients or caregivers. The CGM data from patients using Dexcom CGM were retrieved for three 2-week periods were compared: before the war (1–14 September 2023), after the war outbreak (8–21 October 2023), and 4 months later (1–14 February 2024). Time periods chosen for assessment did not include holiday vacations. Each period reflects a different reality in Israel.

The study was conducted according to the principles of the Declaration of Helsinki and with approval of the institutional ethics committee (TLV-0153-24), which waived patient and parental informed consent.

STUDY POPULATION

Pediatric patients younger than 20 years of age with T1D who were managed by the Institute of Pediatric Endocrinology and Diabetes at Dana-Dwek Children's Hospital were included. The institute’s outpatient clinic manages approximately 400 children, adolescents, and young adults with T1D. We included patients using the Dexcom G6 CGM technology who agreed to share their glucose data with the clinic through the Dexcom Clarity application as part of their routine care. Patients enrolled in the study were treated with either a multiple daily injection (MDI) regimen or insulin delivered via the Omnipod pump (Insulet Corporation, Tel Aviv, Israel), with or without the use of an open-source automated insulin delivery (OS-AID) system. Patients diagnosed with diabetes less than 6 months before the start of the study and patients with insufficient CGM data, as evidenced by CGM active time < 80%, were excluded.

OUTCOME MEASURES

The information retrieved from medical files included sex, age, SEP based on home address [13] and clinical data potentially related to diabetes management such as anthropometric parameters, pubertal stage, celiac disease, and autoimmune thyroid disorder [12]. We also included diabetes-related characteristics: age at T1D diagnosis, diabetic ketoacidosis (DKA) at diagnosis, mode of insulin therapy (MDI, insulin pump, or AID system), total daily insulin dose (units/kg/day), glycemic control (HbA1c values), CGM metrics, and emergency department care for severe hypoglycemia or DKA events.

CGM metrics were retrieved for the three study periods from the ambulatory glucose profile report: time CGM active (%), mean glucose levels (mg/dl), glucose standard deviation (SD) (mg/dl), glucose management indicator (GMI; estimated HbA1c) (%), coefficient of variation (CV), percent time CGM active, time-in-range (TIR: 70–180 mg/dl; 3.9–10 mmol/L), time in tight range (TITR: 70–140 mg/dl; 3.9–7.8 mmol/L), time in hypoglycemia (< 70 mg/dl; < 3.9 mmol/L), time-in-marked-hypoglycemia (< 54 mg/dl; < 3 mmol/L), time-in-hyperglycemia (> 180 mg/dl; > 10 mmol/L), and time-in-severe hyperglycemia (> 250 mg/dl; > 13.3 mmol/L). These definitions are according to the international consensus on CGM interpretation [14].

Capillary HbA1c, anthropometric measurements, and pubertal staging of patients were collected from documentation of in-clinic visits prior to 7 October 2023, as well as from the earliest visit after the start of the war. Z-scores of anthropometric measurements (height and body mass index) were calculated with PediTools Electronic Growth Chart Calculators based on CDC growth charts [15]. Pubertal stage was graded according to the Tanner scale. Puberty onset was defined as Tanner stage 2 in boys with a testicular volume ≥ 4 ml and breast bud appearance in girls. Full puberty was established when pubertal signs matched Tanner stage 5.

Table 1. Sociodemographic and diabetes-related characteristics of children and adolescents at clinic visits before the Iron Swords war

Variable	Value
Number of participants	99
Male, n (%)	52 (52.5)
Age in years, mean ± SD	12.2 ± 4.0
SEP cluster*, mean [IQR]	8 [7–9]
SEP index**, mean [IQR]	1.356 [0.450–1.828]
Co-morbidities	
Celiac disease, n (%)	22 (22.2)
Autoimmune thyroid disease, n (%)	8 (8)
Anthropometric parameters	
Height z-scores	0.27 ± 0.97
Body mass index z-scores	0.10 ± 1.05
Pubertal status***, n (%)	
Prepubertal	45 (45.5)
In puberty	13 (13.1)
Fully pubertal	41 (41.4)
Diabetes-related characteristics	
Age at diagnosis in years, mean ± SD	7.2 ± 3.6
DKA at diagnosis, n (%)	42 (42.4)
Mode of insulin treatment, n (%)	
Multiple daily injections	37 (37.4)
Insulin pump therapy	42 (43.8)
Automated insulin delivery system	20 (20.8)
Daily insulin dose (U/kg/day)	0.8 ± 0.3
HbA1c, mean [IQR]	6.7 [6.2–7.2]

*SEP cluster classifies neighborhoods and localities into clusters, 1 (lowest) and 10 (highest)

**SEP index is an adjusted calculation of 14 variables that measure social and economic levels in four domains: demographics, education, standard of living, and employment

***Pubertal stage was graded according to Tanner stages: Tanner stage 1 = prepubertal, Tanner stages 2 to 4 = in-puberty, and Tanner stage 5 = fully pubertal

DKA = diabetic ketoacidosis, IQR = interquartile range, SD = standard deviation, SEP = socioeconomic position

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 29 (SPSS, IBM Corp, Armonk, NY, USA). All statistical tests were performed as 2-sided. The Kolmogorov–Smirnov test or the Shapiro–Wilk test was performed to analyze the normality of continuous data. Data were expressed as mean ± SD for normally distributed variables and median and interquartile range (IQR) for skewed distribution. The Mann–Whitney test or the Kruskal–Wallis test was used for comparing ordered or quantitative variables, as appropriate. The chi-square test, or Fisher's exact test for small count tables, compared groups in categorical variables. The individual mean values of variables between each pair of time points were compared by a paired *t*-test.

RESULTS

The study cohort comprised 99 children and adolescents (52.5% males), mean age 12.2 ± 4.0 years (range 4.9–19.4 years). The patient characteristics at the in-clinic visit prior to the war are shown in Table 1. The mean anthropometric measurements of the study cohort were within the normal range. Sixty-two patients (62.6%) used insulin pumps, including 20 (32.3%) who used an OS-AID. The mean daily insulin dose was 0.8 ± 0.3 U/kg/day, and the median HbA1c level was 6.7% (6.2–7.2%).

The comparisons between CGM metrics before the war, after the war outbreak, and 4 months later are provided in Table 2. Before the war, the patients had a mean CGM data availability time of 95.4 ± 5.8%. This optimal utilization of the CGM remained unchanged throughout all study periods. The only change observed for the entire cohort was an increase in time-in-severe hyperglycemia following the outbreak of the war (before 12.1 ± 13.9% vs. 13.3 ± 15.9% following the outbreak of the war, $P = 0.05$).

Stratifying the cohort by SEP cluster resulted in 63 patients with higher SEP and 36 with lower SEP, with

Table 2. Comparison of continuous glucose monitoring metrics of patients during the three study periods

	1–14 September 2023 (pre-war)	8–21 October 2023 (war outbreak)	1–14 February 2024	*P1*	*P2*
Time CGM active (%)	95.4 ± 5.8	94.2 ± 9.7	95.2 ± 6.6	0.163	0.309
Mean glucose (mg/dl)	161.2 ± 34.5	160.6 ± 37.4	162.7 ± 34.7	0.747	0.351
Glucose standard deviation (mg/dl)	63.0 ± 17.6	62.4 ± 18.2	64.1 ± 18.2	0.493	**0.047**
Coefficient of variation (%)	38.9 ± 6.3	38.5 ± 6.6	39.2 ± 6.4	0.376	0.157
Glucose management indicator (%)	7.2 ± 0.9	7.2 ± 0.9	7.2 ± 0.8	0.388	0.574
Time in glycemic ranges (%)					
Time-in-range, 70–180 mg/dl	63.6 ± 16.8	63.1 ± 17.8	62.7 ± 17.5	0.601	0.159
Time-in-tight range, 70–140 mg/dl	42.4 ± 14.7	42.9 ± 16.0	42.3 ± 16.1	0.569	0.204
Time < 54 mg/dl	1.1± 1.4	1.2 ± 2.3	0.9 ± 1.6	0.777	0.415
Time < 70 mg/dl	3.4 ± 2.3	3.1 ± 2.9	3.3 ± 2.7	0.196	0.353
Time > 180 mg/dl (%)	20.0 ± 7.0	19.6 ± 8.0	20.2 ± 7.9	0.496	0.249
Time > 250 mg/dl	12.1 ± 13.9	13.3 ± 15.9	12.9 ± 13.6	**0.05**	0.898

*P*1 represents a paired *t*-test comparison between the variable before and after the outbreak of war

*P*2 represents a paired *t*-test comparison between the variable at war outbreak and 4 months after (still during the war)

Bold signifies statistical significance

CGM = continuous glucose monitoring

Figure 1. Mean time spent in glycemic ranges of the cohort of pediatric patients with type 1 diabetes stratified according to socioeconomic position cluster at the three study periods

CGM = continuous glucose monitoring, SEP = socioeconomic position, TITR = time-in-tight range

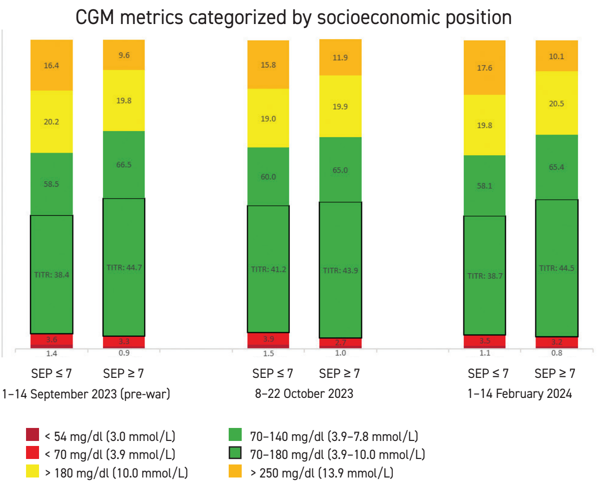
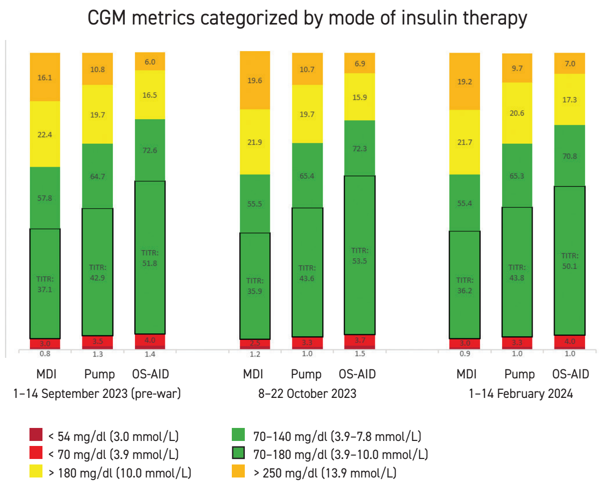


Figure 2. Mean time spent in glycemic ranges of the cohort of pediatric patients with type 1 diabetes stratified according to mode of insulin therapy at the three study periods

MDI = multiple daily injections, OS-AID = open-source automated insulin delivery, TITR = time-in-tight range



a similar mean age for those groups ($P = 0.943$). Figure 1 shows a graphic representation of the mean time spent in different ranges for those two SEP groups at the three study time points. Before the war, patients in the lower SEP group had higher mean glucose levels (170.5 ± 39.3 vs. 155.8 ± 30.6, $P = 0.042$), higher glucose standard deviation levels (69.0 ± 20.9 vs. 59.6 ± 14.6, $P = 0.010$), higher GMIs (7.4 ± 0.9 vs. 7.0 ± 0.7, $P = 0.040$), lower TIRs ($P = 0.022$), lower TITRs ($P = 0.038$), and longer times with severe hyperglycemia ($P = 0.020$) compared to the higher SEP group. Following the outbreak of the war, patients in the lower SEP group showed an increase in TITR (*P* = 0.048), which then decreased 4 months later (*P* = 0.039). Last, patients with higher SEP had an increase in time-in-severe hyperglycemia following the outbreak of the war (*P* = 0.003).

Stratification according to mode of therapy revealed significant differences in CGM metrics at the time point preceding the war. Patients treated by OS-AID had the highest TIRs and TITRs, while patients treated by MDI had the lowest ones (*P* < 0.001 for both parameters). Figure 2 provides a graphic representation of the mean time spent in various ranges for the three therapy groups at the study time points. Following the outbreak of the war, patients treated with MDI had an increase in time-in-severe hyperglycemia (*P* = 0.050). CGM metrics of patients treated by pump with or without OS-AID did not undergo significant changes between the study time points.

No life-threatening events of severe hypoglycemia or DKA were reported during any of the study periods. The comparison of clinical parameters during in-clinic visits before the war outbreak and at the earliest visit afterward showed no significant changes in anthropometric parameters, but there was a significant increase in HbA1c levels (6.76 ± 0.81 vs 7.02 ± 1.07, *P* = 0.005).

DISCUSSION

Children and adolescents with T1D using CGM maintained relatively stable glycemic metrics despite the intense stress of war. A lower SEP and treatment by MDI were associated with poorer CGM metrics and increased susceptibility to changes following the outbreak of the war. Use of CGM allowed for timely treatment adjustments by the patients and/or parents and remote counseling by the medical staff.

The Iron Swords war adversely affected the lives of all Israelis by causing widespread trauma and stress [3]. The emotional distress combined with the avoidance of in-clinic visits due to preferences not to venture far away from the proximity of home bomb shelters may have contributed to significant health deterioration in young patients with T1D. However, our patients did not experience any life-threatening events of severe hypoglycemia or DKA, and they preserved a relatively stable glycemic balance, as observed by their CGM data. The positive impact of CGM can only be achieved with proper use, and its correct utilization remained consistent throughout all study periods.

The benefit of CGM use in patients with T1D during war has been reported in Ukrainian war refugee children [5]. Our finding confirms that, in this era of advancements in diabetes management, the use of technology can help navigate extreme situations [16]. A higher SEP enabled access to essential technologies for effective diabetes management leading to an improved health condition among Ukrainian refugees [17]. Our patients with a higher SEP status showed better pre-war CGM metrics than those with lower SEP. After the onset of the Iron Swords war, CGM metrics remained relatively stable in patients with higher SEP, with some improvement in TIR and TITR among those with lower SEP. This finding corresponds with our earlier report of effective diabetes management in children from extremely low SEP, specifically stateless children born to Eritrean refugees in Tel Aviv, due to Israel's universal health insurance, which ensures equal access to advanced diabetes technology [18].

The mode of insulin therapy affects glycemic control in patients with T1D [19]. We found that patients treated with MDI before the outbreak of the war had the lowest TIRs and TITRs, while patients using OS-AID with the Omnipod insulin pump had the highest TIRs and TITRs. This finding is not surprising and supports previous reports on improvements in time-in-range for patients after the initiation of OS-AIDs [12,20]. After the war started, deterioration in CGM metrics was observed solely in patients who were treated by MDI. These additional advantages could serve to encourage patients to use technologies that adjust insulin delivery based upon CGM input.

Our study has some notable limitations. Since only patients using CGM were included and only short-term data on a given war period are presented, the results may not reflect the glycemic control of individuals with T1D not using CGM. In addition, most of the population treated at our diabetes center resides in central Israel, primarily in the Tel Aviv area, and has a higher SEP (cluster 8). This situation may restrict the study's generalizability and fail to reflect outcomes for patients from other regions of the country. Exploration of the CGM metrics of patients residing in the southern and northern regions of Israel during the war could provide further understanding of the impact of war on diabetes management.

A notable strength of this observational study is the consistent data collection using a single type of CGM. By examining CGM metrics in a real-world setting and without medical interventions, the study findings demonstrate effective management of pediatric patients with T1D during periods of war and limited healthcare access.

CONCLUSIONS

Glycemic control among children and adolescents with T1D using CGM and insulin pump technology remained relatively stable during the outbreak of the Iron Swords war. This finding is reassuring since deterioration of diabetes control has both short- and long-term health implications. Practitioners should therefore maintain a high level of vigilance during stressful conditions to ensure the maintenance of glycemic control in their pediatric patients with T1D.

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History is a novel whose author is the people.

Alfred de Vigny (1797–1863), French poet and early French Romanticist

To be nobody but myself–in a world which is doing its best, night and day, to make you everybody else–means to fight the hardest battle which any human being can fight, and never stop fighting.

E.E. Cummings (1894–1962), American poet, painter, essayist, author, and playwright