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The Effect of Hybrid Closed Loop System Insulin Pump Minimed 780G on The Glycemic Control Compared to Multiple Daily Injections among Type 1 Diabetes Mellitus Children and Adolescents

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Abstract:

Background: Since Food and Drug Administration approved the first Hybrid Closed Loop system in September 2016, more advanced devices have been commercialized. These systems combine insulin infusion with continuous Glucose Monitoring. A Minimed 780G is considered one of the most Advanced Hybrid Closed Loop systems at this time available in pediatric and adult subjects with type 1 diabetes. Previous studies showed an obvious improvement in glycemic parameters in comparison with those traditional ways as multiple dose injection in adults only, not including children. **Objectives:** to compare Glycemic Control among children and adolescents with type 1 Diabetes Mellitus through two methods of treatment: Minimed 780G versus Multiple Daily Injections. **Patients and methods:** This prospective cohort study was conducted on 48 children and adolescents diagnosed with type I Diabetes Mellitus and on Hybrid closed loop system of Minimed 780G or MDI, who were followed in Endocrinology Outpatient clinic at Military Hospitals. The patients were divided into two groups: 32 patients on Multiple Daily Injections and 16 patients on Hybrid Closed Loop System Insulin Pump Minimed 780. **Results:** A significant difference was found between the two groups regarding Pediatric intensive care unit (PICU) admission ($p<0.001$) as it was significantly higher in MDI group than G780 group over a period of six months (from March to August) during 2023. HbA1c readings were significantly higher in MDI group compared to G780 group during the period of study. Cholesterol & triglycerides were significantly higher in MDI group compared to G780 group ($p=0.015$) during 6-month study while no significant differences were found between the two groups regarding very low density, low-density and high-density lipoprotein levels. **Conclusion:** the current study showed that Minimed 780G system resulted in better glycemic control, better lipid profile, lower glycemic variability compared to Multiple Daily Injections among Children and Adolescents with Type 1 diabetes mellitus. Also, Minimed 780G system was associated with lower hospital admission due to Diabetic Ketoacidosis compared to Multiple Daily Injections.

Keywords: Hybrid Closed Loop System, Insulin Pump Minimed 780G on The Glycemic, Multiple Daily Injections, Type 1 D.M, Children, Adolescents

1. INTRODUCTION

Diabetes Mellitus is considered among of the most chronically spread diseases worldwide, with frequency representing 8/100 000 per year among children below the age of 15 years, while it represents 9.3% of the world population. Thus, all nations try to find solutions for patients to cope with life as normal healthy people without feeling any restrictions that affect their future lives **(Patterson *et al.*, 2019).**

Advanced Hybrid Closed Loop Systems merge Automated Basal Rate and correction boluses to help keeping glycemic values within a target range **(Boughton and Hovorka, 2021).** Patients only need to evaluate carbohydrate consumption for meal boluses. Minimed 780G is considered one of the most Advanced Hybrid Closed Loop (AHCL) systems at this time available in pediatric and adult subjects with type 1 diabetes **(de Bock *et al.*, 2018).**

Previous studies showed an obvious improvement in glycemic parameters in which Minimed 780G group can achieve better Time in Range and maintain blood glucose levels within average so it will be more effective in controlling hyperglycemia in comparison with those traditional ways as multiple dose injection among adolescents and adults but studies not including children **(Beato-Víbora *et al.*, 2021).**

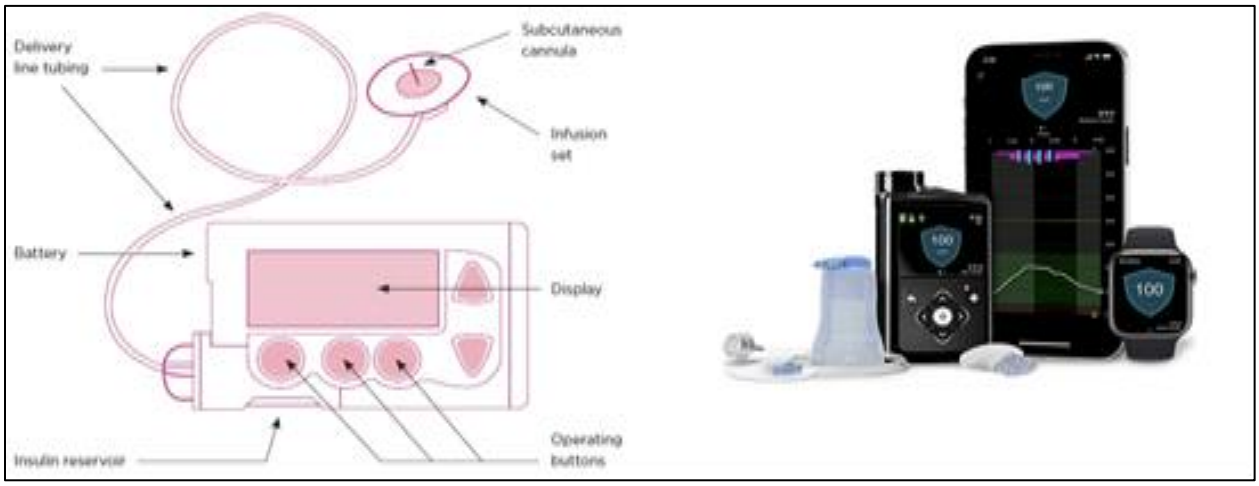

Figure (1): Schematic of the configuration of closed-loop insulin delivery.

Aim of the work

The present study was conducted to compare glycemic and metabolic control in children with type

1 diabetes mellitus on MiniMed 780G and those on multiple dose injection (MDI) during the study period (6 months) by comparing the frequency of hypo and hyperglycemia among children and adolescents with type 1 D.M. on Minimed 780G and those on MDI.

2. PATIENTS AND METHODS

- **Patients**

This prospective observational study was conducted on 48 children and adolescents aged between 5 up to 19 years diagnosed with T1DM. and on HCLS of Minimed 780G or MDI. They were recruited from the endocrinology outpatient clinic of military hospitals (El-Galaa Military Hospital and El-Maadi Military Hospital) during a period of 6 months (from March to August, 2023).

- **Inclusion criteria:**

- Children and adolescents between 5 and 19 years old diagnosed with T1DM. of both genders diagnosed with D.M. for at least six months and either on Minimed 780G or MDI.

- **Exclusion criteria:**

- Patients associated with immunological Disorder (e.g., systemic lupus)
-Patients with other Systemic Diseases (e.g., liver, kidney disease etc.)
- Patients on other medication that could affect results (e.g., systemic glucocorticoids).

- **Sampling**

Sample type: Purposive Sample.

Sample size: According to, **(Petrovski, G. et al. 2022)** the mean HbA1C in patients on Multiple Daily Injections versus Hybrid Closed Loop System Insulin Pump Minimed 780G was8.6±1.7 & 6.5±0.7 respectively. Considering type, I error 0.05 & type II error 0.01 with power of 99%, and confidence level 95%, the minimum required sample size will be 40 patients distributed equally as 20 patients on Multiple Daily Injections and 15 patients on Hybrid ClosedLoop System Insulin Pump Minimed 780G. the sample size was inflated by 20 % to account for the dropout problem in prospective studies

- **Data collection:**

Patients diagnosed with T1DM. at the outpatient clinic were estimated for their Time in Range, Time below Range and Time above Range, recording their RBG in a continuous Glucose Monitoring, being followed up and observed for six months to determine the number of Hypo/Hyperglycemic attacks and whether they suffer from DKA.

- **Methods:**

All patients were subjected to:

Full history taking (e.g., age, sex, anthropometric measures, order of birth, consanguinity, allergy, hospital admission, family history, duration of disease and frequency of hypoglycemic of hyperglycemic attacks)
Full clinical examination to exclude any possible comorbidities.

Investigations include:

- Continuous blood glucose Monitoring for those on Minimed 780G through (T.B.R, T.I.R, T.A.R)
- Pre-prandial and post-prandial Blood Glucose Level for those on M.D.I.
- HbA1C. (3 months prior study and for 6 months)
- Lipid profile

Data analysis:

Data were statistically described in terms of mean ± standard deviation for numerical parametric data, median, and range for non-parametric data, or frequencies and percentages for qualitative data. Student T test or Mann – Whitney test was used for comparison of numerical variables between the study groups. Chi-square test was used for categorical variable. Wilcoxon Signed Rank test was used for subgroup analysis. Spearman rank test was used for correlations between variables. P-values < 0.05 will be considered statistically significant. All statistical calculations were done using SPSS program.

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. The used tests were:

- Chi-square test for categorical variables, to show association between two or more categorical (nominal) variables
- Fisher’s Exact or Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5

- Student t-test for normally distributed quantitative variables, to compare between two studied groups
- Mann Whitney test for not-normally distributed quantitative variables, to compare between two studied groups
- ANOVA with repeated measures for normally distributed quantitative variables, to compare between more than two periods.

3. RESULTS

This study was conducted on 48 children and adolescents diagnosed with T1DM. 16 patients (33.3%) were on HCLS of minimed 780G and 32 patients (67.7%) were on MDI, who presented to Endocrinology Outpatient clinic at Military Hospitals.

- ***Demographic and clinical data of the study group***

Table (1): Comparison between the two groups regarding demographic and clinical data.

		MDI group (N= 32)		G780 group (N= 16)		Test value	P-value
		No.	%	No.	%		
Age (years)	Mean± SD	14.0± 3.23		14.37± 3.22		0.375	0.707 (NS)
	Median (IQR)	14.5 (12- 17)		14.5 (12- 17)			
	Range	7 – 18		6 – 18			

		No.	%	No.	%		
Consanguinity of parents	Negative	31	96.9%	16	100.0 %	X^2= 0.511	>0.999^{FET} (NS)
	Positive	1	3.1%	0	0.0 %		
History of NICU admission	No	31	96.9%	16	100.0 %	X^2= 0.128	1.00^{FET} (NS)
	Yes (due to jaundice)	1	3.1%	0	0.0 %		
Vaccination	Up to date	32	100.0%	15	93.8%	X^2= 2.043	0.333^{FET} (NS)
	Not all vaccines as patient was living outside Egypt	0	0.0%	1	MW 6.3 %		
Family history Of Diabetes	Negative	27	84.4%	16	100.0 %	X^2= 1.367	0.242 (NS)
	Positive	5	15.6%	0	0.0 %		
Developmental history	Normal	32	100.0%	15	93.8%	X^2= 2.043	0.333^{FET} (NS)
	Abnormal	0	0.0%	1	6.3 %		

		MDI group (N= 32)		G780 group (N= 16)		*Chi- Square test*	
		No.	%	No.	%	Test value (X^2)	P-value
Allergy	No	29	90.6%	16	100.0%	0.400	0.541^{FET}(NS)
	Yes	3	9.4%	0	0.0%		
	Cow milk protein allergy	2	%6.3	0	0.0%		
	positive for animal hair	1	3.1%	0	0.0%		

ext: 28609

In MDI group, the mean age was 14.0± 3.23 years, (68.8%) of them were males while in G780 group, the mean age of 14.37± 3.22 years, (62.5%). non-significant difference was found between the two groups regarding age as shown in **figure (1).**

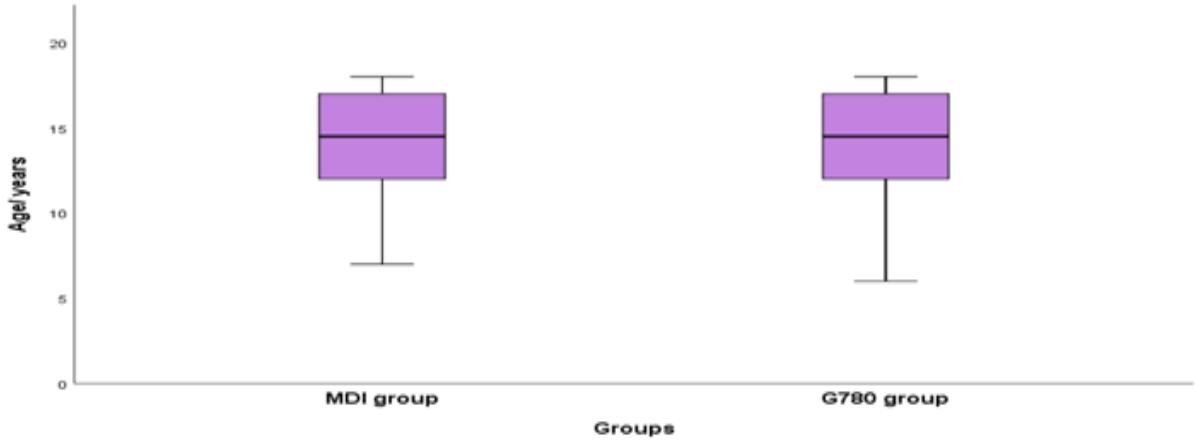

Figure (1): Comparison between study groups regarding age.

There was no statistically significant difference between the two groups regarding consanguinity, history of NICU admission, vaccination, family and developmental history (P > 0.05)**.** No significant difference was found between MDI group and G780 group regarding allergy (p>0.05) as shown in **table (1)**.

In MDI group, the mean DM duration was 6.58± 2.49 years while in G780 group, the mean DM duration of 6.66± 2.74 years. No significant difference was found between the two groups regarding DM duration (p>0.05) as shown in **figure (2)**.

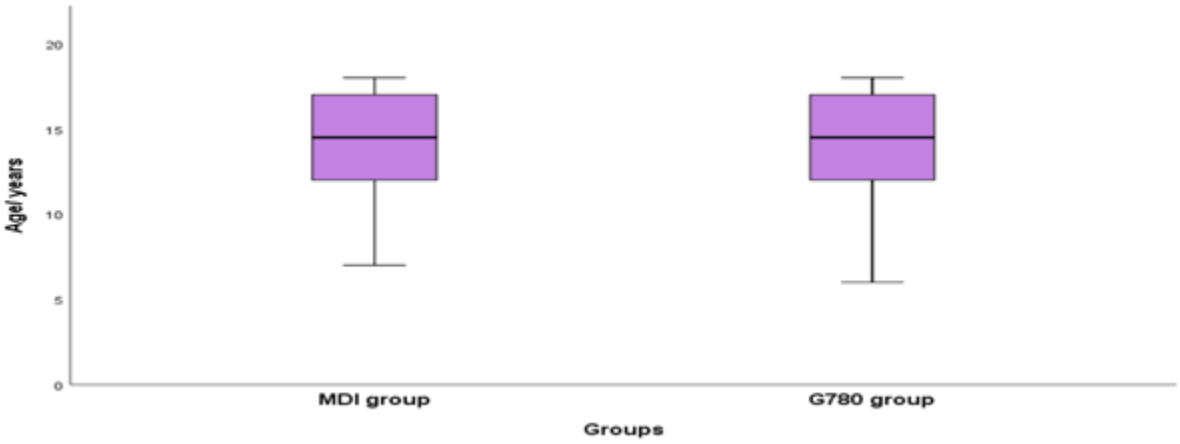

Figure (2) Comparison between study groups regarding DM duration.

In MDI group, 27 (84.4%) cases reported PICU admission for DKA with mean duration of 2.0± 1.26 days. A significant difference was found between the two groups regarding PICU admission (p<0.001) as it was significantly higher in MDI group than G780 group as shown in **table (1)**.

- ***Laboratory data of the study group***

Table (2): HbA1c and Lipid profile among the studied groups at different follow up times.

		MDI group (N= 32)			G780 group (N= 16)			Test value	P-value
		Mean	±SD	Range	Mean	±SD	Range		
HbA1c	1st reading	9.07	±2.27	5.2 - 14.0	7.99	±1.06	5.9 -11.0	T= 2.220	**0.032(S)**
	2nd reading	8.34	±1.75	4.9 - 13.2	7.27	±0.77	6.3 -8.8	T= 2.315	**0.006 (HS)**
	3rd reading	8.80	±2.40	3.0 - 15.7	7.16	±0.78	6.0 -9.0	T= 2.652	**0.011(S)**
	4th reading	8.57	±1.69	7.4 - 10.5	8.00	±0.0	8.0 -8.0	T= 2.345	0.144 (NS)
p-value#		0.241 (NS)			0.392 (NS)				
Cholesterol (mg/dl)		164.81	±38.87	102.0 -254.0	133.75	±39.54	87.0 -209.0	T= 2.595	**0.015 (S)**
TGs (mg/dl)		110.12	±112.5	36.00 -608.0	62.75	±17.39	31.0 -97.0	T= 2.328	**0.026 (S)**
VLDL (mg/dl)		22.33	±21.24	7.0 -116.0	20.81	±10.76	6.0 -46.0	T= 0.268	0.790 (NS)
HDL (mg/dl)		56.70	±14.5	27.0 -85.0	52.63	±8.21	28.0 -61.0	T= 1.242	0.221 (NS)
LDL (mg/dl)		92.22	±26.83	42.0 -150.0	86.00	±31.12	29.0 -139.0	T= 0.718	0.477 (NS)

Cholesterol & triglycerides were significantly higher in MDI group compared to G780 group (p=0.015) at the time of the study while no significant differences were found between the two groups regarding VLDL, LDL and HDL levels (p>0.05) as shown in **table 2**

HbA1c at 1st 2nd and 3rd reading was significantly higher in MDI group compared to G780 group during the period of study**.**

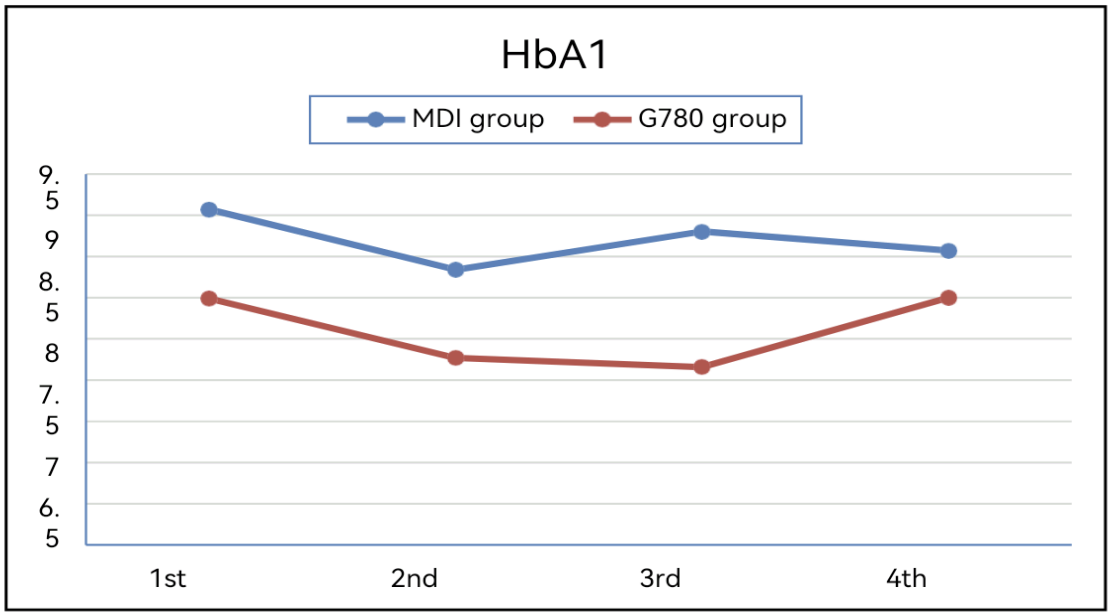

Figure (3): HbA1c at different follow up periods in the study.

Table (3): Time in range, time above range and time below range in G780 group.

	G780 group (N= 16)		
	Mean	±SD	Range
TIR	73.38%	±11.00%	46.00% -89.00%
TAR	24.06%	±11.11%	10.00% -53.00%
TBR	2.56%	±1.79%	0.00% -5.00%

SD: standard deviation, TBR: time below target range, TAR:Time above range , TIR :Time in Rang

In G780 group, the mean TIR was73.38% ±11.00% mean TAR was 24.06%± 11.11% while the mean TBR was2.56%± 1.79% during a 6 month period of study for patients at least already on G780 for about 6 months before our study began and that was shown in **table (3).**

Table (4): Blood glucose level among MDI group.

	MDI group (N= 32)	
	Mean ±SD	**Range**
pre-prandial breakfast	97.41 ±25.83	72.0 ±187.0
2-hr post prandial breakfast	167.09 ±21.55	126.0 ±204.0
pre-prandial lunch	100.09 ±18.41	75.0 ±148.0
2-hr post prandial lunch	195.62 ±32.93	110.0 ±293.0
pre-prandial dinner	110.91 ±22.73	78.0 ±178.0
2-hr post prandial dinner	153.16 ±35.84	77.0 ±225.0
hypo-glycemic attacks	6.97 ±3.47	3.0 ±19.0
hyperglycemic attacks	22.19 ±7.20	11.0 ±37.0

In MDI group, the mean pre-prandial breakfast glucose was 97.41±25.83 mg/dl, while the mean 2-hr post prandial breakfast was 167.09±21.55 mg/dl.

The mean pre-prandial lunch glucose was 100.09±18.41 mg/dl, while the mean 2-hr post prandial lunch was 195.62±32.93 mg/dl.

The mean pre-prandial dinner glucose was 110.91±22.73 mg/dl, while the mean 2-hr post prandial dinner was 153.16±35.84 mg/dl.

The mean number of hypo-glycemic attacks was 6.97±3.47, while the mean number of hyper-glycemic attacks was 22.19 ±7.20 during 6-month period of study and that is shown in **table (4).**

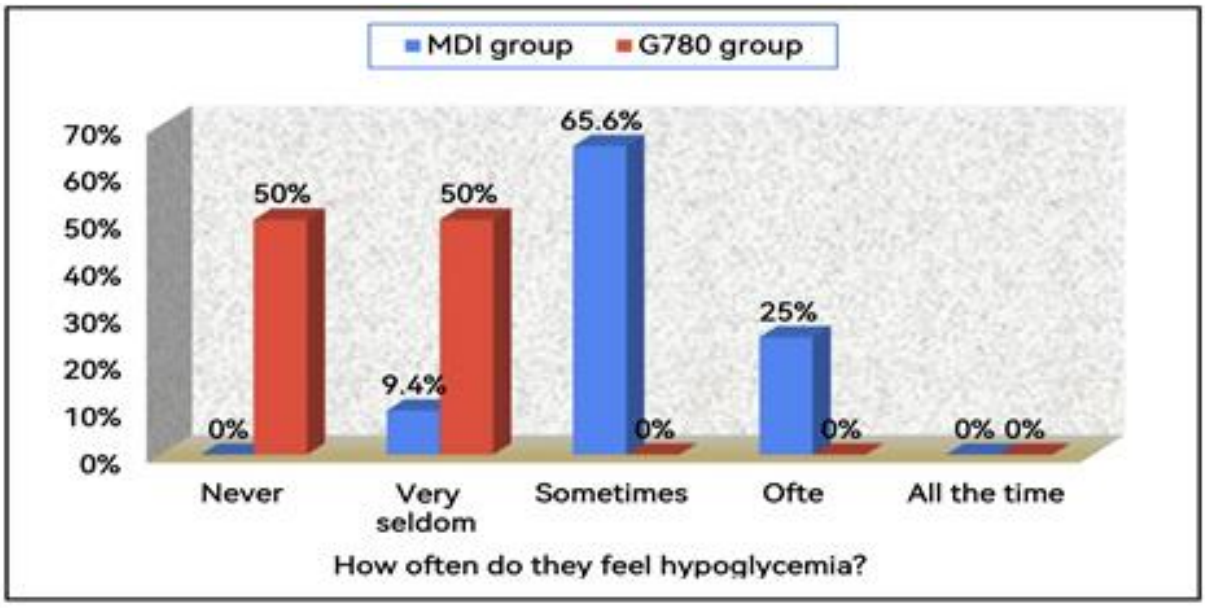

Figure 4 : Comparison between the two studied groups regarding how often they feel hypoglycemia.

In MDI group, 9.4% patients very seldom had hypoglycemic attacks, 65.6% sometimes had hypoglycemia and 25% of them often had hypoglycemic attacks. While in G780 group, 50% patients never had low blood sugar, and 50% very seldom had low blood sugar.

4. DISCUSSION

T1DM is a chronic disease, requiring appropriate metabolic control in pediatric patients to prevent or delay the onset of related complications **(Bebu et al., 2020).**

According to **(Miller et al.,2015),** a significant percentage of individuals with T1DM do not meet their glycemic targets, suggesting that novel strategies are needed for optimum metabolic control. The high burden of managing diabetes stems from the necessity for frequent decisions on insulin dose that impact insulin sensitivity and glucose levels in order to prevent hypoglycemia in T1DM **(Ruan et al., 2016)**. This leads to daily variability in insulin demand and glucose levels.

In order to prevent both hypoglycemia and hyperglycemia, hybrid closed loop systems use specialized control algorithms that automate basal insulin delivery based on glucose sensor measurements **(Weisman et al., 2017) (Biester et al., 2019).**

The MiniMed 780G system (Medtronic, Northridge, CA, USA) is one of the newest HCL systems; it went on sale in a few countries in October 2020. When necessary, this device provides an automated bolus correction in addition to automatically giving basal insulin with a glucose target that can be customized (**Petrovski et al., 2022)**.

The main aim of this study was to compare Glycemic Control between Minimed 780G and Multiple Daily Injections among children and adolescents with type 1 DM. This prospective study was conducted on 48 children and adolescents diagnosed with T1DM. and on HCLS of minimed 780G or MDI, who admitted to Endocrinology Outpatient clinic at Military Hospitals.

The patients were divided into two groups: 32 patients on Multiple Daily Injections and 16 patients on Hybrid Closed Loop System Insulin Pump Minimed 780G.

To eliminate the contribution of any confounding factor that may affect the final outcome the current study enrolled two well-matched groups in baseline data, as there was no statistically significant difference between the studied groups as regard age, clinical history, complaints, allergy and DM duration.

Regarding hospital admission among the studied groups, the current study showed that in MDI group, 27 (84.4%) cases reported PICU admission for DKA with mean duration of 2.0± 1.26 days. A significant difference was found between the two groups regarding PICU admission ($p<0.001$) as it was significantly higher in MDI group than G780 group.

So, our results showed that the use of AHCL Minimed 780G resulted no any episodes of severe hypoglycemia or diabetic ketoacidosis necessitating hospital admissions. This comes in agreement with **Petrovski et al. (2022)** who aimed to evaluate the glycemic outcomes in 34 children and adolescents with T1DM previously treated with MDI using a structured initiation protocol for the AHCL Minimed 780G insulin pump system and reported no episodes of severe hypoglycemia or DKA with no hospital admissions. Also, **Matejko et al. (2022)** reported no events of severe hypoglycemia or diabetic ketoacidosis among 20 T1DM adults with MiniMed 780G advanced hybrid closed-loop (AHCL) system or MDI over 3 months follow-up.

Regarding HbA1c among the studied groups at different follow up times, our study revealed that HbA1c at 1st, 2nd and 3rd readings were significantly higher in MDI group compared to G780 group. In concordance with the current study **Matejko et al. (2022)** who revealed that G780 system have significantly lower HbA1c than patients MDI treatment at 3 months post treatment. Moreover, **Tornese et al. (2021)** showed that 780G system users had a significantly lower HbA1c compared to MiniMed™ 670G system after six months of HCL use (7.1 vs. 7.7%).

Regarding lipid profile among the studied groups, the current study showed that cholesterol & triglycerides were significantly higher in MDI group compared to G780 group (p=0.015) while no significant differences were found between the two groups regarding VLDL, LDL and HDL levels (p>0.05). Several studies reported that there was significant association between lipid profile glycemic control, **Zabeen et al. (2018)** revealed that there was positive association between high TG, TC, and low HDL and poor glycemic control. Consequently, our results suggested that G780 group have significantly better lipid profile (and consequently better glycemic control) than patients MDI group.

Regarding time in, above and below range in G780 group, the current study showed that the mean TIR was 73.38%±11.00%, mean TAR was 24.06%± 11.11% while the mean TBR was2.56%± 1.79%. Comparable with the current study **Petrovski et al. (2022)** showed that TIR increased from 42.1±18.7% at baseline to 78.8±6.1% in the study phase (p< 0.001) among patients underwent AHCL Minimed 780G treatment. Also, the randomize controlled study by **Matejko et al. (2022)** showed that the mean TIR increased significantly (P < 0.001) from 69.3 ±12.3% at baseline to 85.0 ± 6.3% at 3 months in the Minimed 780G group, while remaining unchanged in the MDI group (P = 0.684): 62.8 ± 10.7% to 61.5 ± 11.2%. All participants in the AHCL group (20 of 20) achieved a TIR >70%, compared with 29.4% (5 of 17) in the MDI group (P < 0.001).

Regarding blood glucose level among MDI group, it was revealed that the mean pre-prandial breakfast glucose was 97.41±25.83 mg/dl, while the mean 2-hr post prandial breakfast was 167.09±21.55 mg/dl. The mean pre-prandial lunch glucose was 100.09±18.41 mg/dl, while the mean 2-hr post prandial lunch was 195.62±32.93 mg/dl. The mean pre-prandial dinner glucose was 110.91±22.73 mg/dl, while the mean 2-hr post prandial dinner was 153.16±35.84 mg/dl. The

mean number of hypo-glycemic attacks was 6.97±3.47, while the mean number of hyper-glycemic attacks was 22.19±7.20.

The above results showed high variability of glucose level through the day and high incidence of hyper-glycemic attacks as well as hypo-glycemic attacks. This was supported by **Matejko et al. (2022)** the findings by who revealed that the MDI with self-monitoring of blood glucose was associated with higher rate of glucose variability compared to MiniMed 780G system ($p<0.001$). Previous studies on 780G system showed a reduction in the variability of the outcomes achieved across different countries and across different age groups **Carlson et al.,2021,**

Moreover, most of the glycemic parameters showed an important further advanced improvement up to the end of the 6month study period which was confirmed by a significant progressive reduction in the HbA1c values (0.5% at 3 and 0.7% at 6 months follow up). The effectiveness of Medtronic 780G appeared even more remarkable: before Medtronic 780G all the patients used a CGM and 51/59 an insulin pump, without severe hyperglycemia (mean HbA1c of 7.5%). A similar decrease in HbA1c (−0.4%) had been formerly observed after Medtronic 670G but in a population that did not use CGM in basal condition **(McAuley *et al.* 2020,**

These clinical outcomes agreed with the high sensor and AHCL usage. The new algorithm with automated correction boluses and more stringent Improved TIR and a higher proportion of time spent in AHCL were the results of more strong tailoring of the therapy made possible by the pump settings (AIT of 2-3 h and algorithm glucose goal of 100 mg/dl and 110 mg/dl. The success of the current AHCL system is probably largely due to the fact that there are fewer exits from AHCL usage than there were in the prior Minimed 670G HCL system **(Petrovski *et al.*, 2020).**

optimizing glucose target and active insulin time, modifying ICR, automating bolus correction in addition to automated basal insulin delivery, and effectively distributing insulin delivery based on each patient's unique needs, improved glycemic outcomes were achieved with a minimal increase in total insulin dose **(Bergenstal *et al*.2020), .**

5. CONCLUSION

The current study showed that Minimed 780G system resulted in better glycemic control with better lipid profile when compared to Multiple Daily Injections among Children and Adolescents T1DM. Also, Minimed 780G system was associated with less hospital admission due to Diabetic Ketoacidosis compared to Multiple Daily Injections.

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The researcher did not receive any specific funding for this study.

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