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Application of Continuous Glucose Monitoring Systems in Patients With Type 2 Diabetes Mellitus

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Abstract

Though continuous glucose monitoring systems (CGMS) have proven their benefits in type 1 diabetes mellitus, research about their use in type 2 diabetes mellitus (T2D) are still in progress. The current study aimed to evaluate the use of such systems in patients with T2D in comparison with the standard periodic capillary measurements. Twenty-five patients with T2D under insulin or combination of insulin and oral medication participated in a prospective 7-day observational study. American Diabetes Association 2021 targets for good euglycemic control were used as primary goals for the two groups (CGMS over capillary measurements). Seventy two percent of the participant achieved maintenance of blood glucose within therapy target guidelines. Moreover, 64 % of the participants achieved glycohemoglobin HbA1c < 6.5 %.

Glucose values with both methods display high level of correlation ((r = 0.901, p < 0.001) and the same is also valid for HbA1c and estimated HbA1c ((r = 0.939, p < 0.001). Thus, CGMS can achieve both better glycemic control and decrease of HbA1c in patients with T2D. Though the present findings are in accordance with the available literature, further studies in larger populations with more deeper analyses are still needed to confirm the usefulness of CGMS in T2D.

Keywords: continuous glucose monitoring systems, type 2 diabetes mellitus.

1. Introduction

Though COVID-19 pandemic had dominated medical interest in the last 2 years, managing of diabetes mellitus (DM) continues to pose a great challenge. DM global burden constantly rises and prognosis about the future is worsening (IDF Atlas, 2019). Technology advance has created a new branch in DM management that facilitates both monitoring (continuous monitoring systems - CGMS, their flash and total implantable variants) and therapy (with subcutaneous continuous insulin infusionsystems) (Kravarusic et al., 2020). And though CGMS has proven their benefits in type 1 DM (T1D) (Carlson et al., 2017), research about their use in type 2 DM (T2D) are still in

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progress. Results from studies like DIAMOND (Ruedy et al., 2017) or GP-OSMOTIC (Furler et al., 2020) are promising, and systemic reviews are planning for the near future (Zheng et al., 2020).

Within this frame, the current study aimed to evaluate the use of CGMS in patients with T2D in comparison with the standard periodic capillary measurements.

2. Materials and methods

The study took place in Diabetic Unit Care, AHEPA University Hospital, Thessaloniki, Greece from 01/09/2020 – 01/12/2020. Twenty-five (25) patients with T2D under insulin or combination of insulin and oral medication participated in a prospective observational study. Exclusion criteria included: Type 1 diabetes mellitus, specific diabetes types: pregnancy-related, drug or toxin–induced diabetes, endocrinopathy-associated diabetes, patients with acute renal failure or chronic renal failure in hemodialysis, women in reproductive age and any hyperglycemic emergencies (e.g. diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic syndrome). Informed consent was obtained from all participants.

After full medical history interview and clinical examination, a CGMS sensor (Enlite™ Glucose Sensor, Medtronic SA, Ireland) was applied according to manufacturer's guidelines for a period of 7 days. During study period CGMS recorded 588 measurements in each participant. Along with Glu measurements both from CGMS and capillary blood, CGM parameters (Envision™ Pro CGM System, Medtronic SA, Ireland) such time in range (TIR) (time interval with Glu falling within 70-140 mg/dl), time above range (TAR) (time interval with Glu recordings > 140 mg/dl), time below range (TBR) (time interval with Glu recordings < 70 mg/dl), area under curve (AUC) form Glu values > 140mg/dl and < 70 mg/dl were also recorded. Demographics parameters (age, sex, body weight, BMI), selected blood count parameters (white blood cells-WBC, hemoglobin-Hb, platelets – PLT), glycohemoglobin (HbA1c), urea, creatinine, total cholesterol (Chol) and its high- and low-density fractions (HDL, LDL), lactate dehydrogenase (LDH) and hepatic transaminases (SGOT, SGPT) were also measured. American Diabetes Association 2021 targets for good euglycemic control were used as primary goals for the two groups (American Diabetes Association, 2021).

Data analysis was conducted with SPPS® Statistics for Windows, v.24.0 (IBM Corp. Armonk, NY, USA) and included exploratory descriptive analysis, data normality evaluation (using Kolmogorov-Smirnov test), comparison test (Student's t-test or Mann Whitney U test) and correlation coefficient calculation (Pearson coefficient r^2). Statistical significance level was defined as $p < 0.05$.

3. Results

Data from all 25 patients (15 men and 10 women) were included for further analysis, as no problems/complications were reported during the use of CGMS. Women were elder and shorter than men, yet with almost the same BMI (Table 1).

Table 1. Demographics characteristics of the participants. Data are presented in form of mean (standard deviation). Statistical significance $p < 0.05$

Parameters/Patients	All (n = 25)	Men(n = 15)	Women (n = 10)	p
Age (years)	68.3(11.3)	64.1 (10.3)	74.7 (9.9)	0.017
Weight (kg)	84 (25.5)	84 (25)	77 (28.5)	0.091*
Height (cm)	172.2 (10.4)	175 (13)	165 (9.3)	< 0.001*
BMI (kg/m^2)	27.6 (4.2)	27.6 (4.39)	29.42(8.85)	0.495*

*Mann-Whitney U test

Antidiabetic regiment varied among participants: 40 % of them (10/25) received monotherapy (metformin or dipeptidylpeptidase-4 (DDP-4) inhibitors), 24 % (6/25) received

double therapy, 24 % (6/25) received triple drug regiment and 12 % (3/25) received a combination of four drugs. Only 12 % (3/25) received insulin and 16 % (4/25) a combination (Table 2).

Table 2. Detailed presentation of antidiabetic regiment: SGLT2 – Sodium-glucose cotransporter 2 inhibitors, DDP – 4 inhibitors – Dipeptidyl peptidase – 4 inhibitors, GLP-1, Glucagon-like peptide-1 receptor agonists.

Regiment	All	Men	Women
Metformin	7	3	4
Bigouanide	1	0	1
DDP-4 inh.	2	1	1
DDP-4 inh./Metformin	4	2	2
SGLT-2/Metformin	2	2	0
DDP-4 inh./Metformin/SGLT-2	2	2	0
DDP-4 inh./Metformin/Pioglitazone	1	0	1
DDP-4 inh./Bigouanide/SGLT-2	2	0	1
DDP-4 inh./Metformin/SGLT-2/Pioglitazone	1	1	0
DDP-4 inh./Metformin/SGLT-2/Insulin	1	1	0
SGLT-2/Metformin/Insulin/GLP-1	1	1	0
DDP-4 inh./Metformin/SGLT-2/Sulphonylureas	1	1	0

Twenty eight percent (28 % or 7/25) of the participants had diabetic neuropathy, 76 % (19/25) was under antihypertensive therapy and 64 % (16/25) was receiving also antilipidemic drugs. Antihypertensive regiments included β-blockers, hydrochlorothiazides, angiotensin-converting-enzyme (ACE) inhibitors, Calcium channel blockers and ACE 2 receptors blockers. Dyslipidaemia therapy included statins (atorvastatin, rosuvastatin, simvastatin) or statin-ezetimibe and statin-fibrate combinations.

Most laboratory measurements were the same in both men and women, apart from HDL, Hct and liver transaminases (Table 3).

Table 3. Laboratory characteristic of the participants. Presented in mean (standard deviation-sd) form

	All	Men	Women	p
Ur(mg/dl)	39.1 (7.3)	39.5 (7.7)	38.4 (7.1)	0.713
Cr (mg/dl)	0.9 (0.3)	1 (0.2)	1.3 (1.6)	0.451
Chol tot (mg/dl)	150.1 (17.6)	146.4 (13.3)	155.7 (22.3)	0.203

HDL (mg/dl)	42.8 (6.4)	40.5 (6)	46.1 (5.5)	0.028
LDL (mg/dl)	92.8 (19.6)	89.3 (13.4)	97.9 (26.3)	0.294
Try (mg/dl)	137.7 (42.8)	143.1 (47.1)	129.5 (36.3)	0.448
SGOT (U/l)	29.6 (11.1)	34 (9.5)	22.9 (10.1)	0.011
SGPT (U/l)	31 (10.5)	35.7 (7.2)	23.9 (10.9)	0.003
WBC (mg/dl)	6372 (1389.7)	6460 (1611)	6240 (1039.4)	0.707
Hgb (g/dl)	13.2 (0.9)	13.5 (0.7)	12.8 (1.1)	0.091
Hct (%)	40.5 (2.4)	41.2 (1.9)	39.3 (2.6)	0.049
PLT (K/µL)	235.4 (51.2)	232.5 (55.4)	239.9 (46.6)	0.730

CGMS parameters along with HbA1c and capillary blood measurement are displayed in Table 5.

Table 4. CGSM parameters, capillary blood glucose measurement (Glu_c) and HbA1c in form of mean (standard deviation)

Parameter	All	Men	Women	p
HbA1c (%)	6.3 (1.1	6.3 (0.7)	6.1 (0.3)	**0.048** *
eHbA1c (%)	6.5 (1.7)	6.6 (0.9)	6.15 (1.7)	0.091*
Glu $_{CGMS}$ (mg/dl)	140 (48)	142 (26)	129.5 (48.3)	0.115*
Glu $_{CGMS}$ Max	252.7 (60.3)	254 (47)	212 (98)	0.080*
Glu $_{CGMS}$ Min	86 (24.5)	77 (31)	87.5 (21.5)	1*
TIR(%)	70 (50.5)	70 (27)	82 (43.5)	0.062*
TAR (%)	29 (50.5)	30 (27)	18 (45)	0.062*
TBR (%)	0.3 (0.6)	0.46 (0.7)	0.25 (0.7)	0.567*
Total TAR time (min)	2710 (3228)	2880 (4740)	1370 (2593)	**0.040** *
Total TBR time (min)	21.8 (53.1)	27 (59.2)	14 (44.3)	0.361*
Total TIR (min)	6970 (3540)	5990 (4773)	8065 (3521)	0.096*
TAR/day (min)	387.1 (461.1)	411.4(677.1)	195.7 (370.4)	0.096*
TBR time/day (min)	3.1 (7.6)	3.9 (8.5)	2 (6.3)	0.361*

TIR time/day (min)	995.7 (505.7)	855.7 (681.9)	1152.1 (503.4)	**0.041***
AUC >140	7.4 (23.5)	8.5 (10.2)	3.85 (20.8)	**0.031***
AUC <70	0.02(0.04)	0.027 (0.5)	0.013 (0.4)	0.600*
High exceedances (frequency)	13.4 (7.6)	14.9 (7.8)	14.4 (6.4)	0.621
Low exceedances (frequency)	0.96(2.6)	1.7 (3.6)	0.6 (1.8)	0.488
Glu_c Day 1	150 (81)	152 (120)	126.5 (48.8)	0.291*
Glu_cDay 2	148 (36)	152 (66)	134 (31.5)	**0.024***
Glu_c Day 3	144 (55)	148 (87)	124.5 (55)	0.120*
Glu_c Day 4	124 (65)	136 (118)	105 (35.8)	**0.026***
Glu_c Day 5	120 (56)	139 (54)	109.5 (18.3)	**0.021***
Glu_c Day 6	132 (42.5)	138 (75)	106.5 (40.5)	**0.035***
Glu_cDay 7	124 (56)	142 (72)	109.5 (40.5)	**0.037***
7-days Glu_c mean	133.4 (47.79)	144.4 (90.29)	112.86 (38.93)	**0.052***

According to ADA 2021 guidelines, 72 % of the participant achieved good glycemic control. Moreover, 64 % of the participants achieved HbA1c < 6.5 %.

Finally, Glu_{CGMS} and Glu_c values display high level of correlation ($r = 0.901$, $p < 0.001$) and the same is also valid for HbA1c and eHbA1c ($r = 0.939$, $p < 0.001$)

4. Discussion

The most important finding of this study is the success of glycemic control in 72 % and the achievement of HbA1c < 6.5 % in 64 % of participants. These results come as addition to available literature. Though data for T2D patients are more limited than for patients with T1D, there is evidence of greater benefits of CGMS over other measurements, for patients receiving multiple insulin injections or other regimens (Beck et al., 2020; Ehrhardt et al., 2011). In a recent, 52-week randomized trial in patients with T2D treated with various regimens, the mean reduction in HbA1c at 12 weeks was 1.0 % (sd 1.1 %) with CGMS for four cycles of 2 weeks and 5 % (sd 0.8 %) with self-monitoring blood glucose ($p = 0.006$) (Ehrhardt et al.., 2011). Previously, Yoo et al (Yoo et al., 2008) studied 65 patients with poorly controlled T2D in a variety of treatments and the use of CGMS resulted in a 0.7 % reduction in HbA1c in the intervention group compared with the group randomized to self-monitoring blood glucose.

Beck et al (Beck et al., 2020) randomized study evaluated the benefit of CGM use in 158 T2D patients with mean HbA1c of 8.5 % treated using multiple daily injections. Again, HbA1c decreased to 7.7 % in the CGM group over a 24-week period compared to 8 % in the group with usual care. Furthermore, Craciun et al included 28 patients with T2D to evaluate the impact of short-time CGM on glycemic control and found that HbA1c decreased significantly from 8.8 % at baseline to 7.3 % at follow-up ($p < 0.0001$) in the whole group (Cracium et al., 2014).

Limitation of the available findings (most of the studies are single center, with relatively small sample and lack of cohort-of-interest analyses) may decrease their importance; yet a clear trend seems to be forming. Despite the contradictory or unclear effects of CGM use for patients with T2D and the lack of relevant studies, clinical trial results have shown that the use of CGMS not only reduces HbA1c and hypoglycemia but can alleviate the fear of hypoglycemia and anxiety associated with DM and improve quality of life (Kubiak et al., 2016; Patton et al., 2016). Thus, CGMS are gaining ground among patients as they provide significant benefits ,i.e. comprehensive picture of glycemic variability and connection of glucose excursions with meals, exercise, sleep and medication; information that can enhance the management of DM (Danne et al., 2017).Unfortunately, their extremely high relative cost limits their use only to selected clinical scenarios (Vashist et al., 2013). As technology progresses, larger availability of CGMS may also become more accessible.

5. Conclusion

CGMS can achieve both better glycemic control and decrease of HbA1c in patients with T2D. Yet, further studies in larger populations with more deeper analyses are still needed to confirm this finding.

6. Conflict of interests

The authors have no conflicts of interest to declare.

7. Authors' Contributions

A.M conceptualization, design of the study, data recording and analysis, oral presentation, T.A. literature review, final draft writing, D.T. design of the study, supervision, S.C,K.F literature review, supervision. All authors have reviewed and agree with the final manuscript.

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None.

Ethical approval and consent to participate.

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