EFFICACY AND SAFETY OF CONTINUOUS GLUCOSE MONITORING SYSTEMS VS. SELF-MONITORING BLOOD GLUCOSE IN PATIENTS WITH TYPE 1 DIABETES MELLITUS. A SYSTEMATIC REVIEW AND META-ANALYSIS.

Project financed by ***Medtronic Poland Sp. z o.o.***

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Introduction

- It has been demonstrated that a glycemic control reduces the risk of diabetes mellitus long-term complications.
- The use of continuous glucose monitoring (CGM) systems combined with self-monitoring blood glucose (SMBG) may improve metabolic control.
- Recently, efficacy of CGM has been assessed in numerous clinical trials directed at evaluating glycemia level.
- The aim of the study was to present the current knowledge on the impact of CGM combined with SMBG compared to SMBG alone on improving glycemic control in type 1 diabetes mellitus (T1DM).

Methods

Systematic literature search

- A systematic literature search was performed in order to identify studies fulfilling the inclusion criteria:
  - *Population*: T1DM patients staying on intensive insulin regimen maintained either continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI),
  - *Comparison*: CGM + SMBG vs. SMBG; the same insulin regimen in both arms was required,
  - *Efficacy measurements*: HbA_{1c} change from baseline, HbA_{1c} at follow up, percentage of patients with target HbA_{1c} level, HbA_{1c} reduction, daytime glycemia, nocturnal glycemia, all hypo/hyperglycemic episodes; duration of severe hypo/hyperglycemic episodes,
  - *Safety measurements*: mortality, ketoacidosis episodes, adverse events, treatment discontinuations, CGM system irregularities,
  - *Methods*: randomized controlled trials (RCTs),
  - *Exclusion criteria*: intensive care unit, intraperitoneal insulin infusion, non-invasive CGM systems, CGM prototypes and assessments of mathematic models/software used in CGM systems, studies published only in abstract form, studies in languages other than Polish, English, French or German.
- Following databases and sources were searched: MEDLINE, EMBASE, The Cochrane Library, Trip Database, Centre for Reviews and Dissemination, registers of clinical trials, meeting abstracts from the European Association for the Study of Diabetes, websites of the International Network of Agencies for Health Technology Assessment (INAHTA), sources provided by FDA, EMEA, TGA. The reference lists of publications identified from the initial electronic search were also screened. The last search was performed in January 2010.
- Two authors independently reviewed the articles at each stage of the selection. Disagreements were solved by consensus.

Statistical analyses

- Results for respective endpoints are expressed as odds ratio (OR) for dichotomous endpoints and standardized medium difference (SMD) or weighed medium difference (WMD) for continuous endpoints.
- In case of lack of statistically significant heterogeneity of data, meta-analysis was performed using Mantel-Haenszel fixed effect model. DerSimonian-Laird random effect model was used when data heterogeneity was present.
- Result are presented with 95% confidence intervals and were considered statistically significant when $p \leq 0.05$.

Results

- Thirteen RCTs were identified that included a total number of 1125 patients with type 1 diabetes mellitus followed for at least 3 months.
- Eleven trials investigated patients with T1DM and 2 trials patients with T1DM or T2DM, with separate results for both groups (Table 1).
- Studies differed with regard to the patients age (children, adolescents, adults), CGM system manufacturer (Medtronic, Menari Diagnostics, DexCom, Abbott Diabetes Care), integration with the insulin pump (integrated vs. non-integrated) and insulin regimen (CSII vs. MDI).

Change in HbA_{1c} level

- Change in HbA_{1c} from baseline values was assessed in all 13 studies included in the analysis. Four trials (Beck 2009, Deiss 2006b, O'Connell 2009 and Tamborlane 2008) demonstrated superiority of CGM system, remaining 9 studies did not show statistically significant differences.
- Pooled data of 13 trials revealed significant reduction of HbA_{1c} level in CGM group compared with control group (WMD = -0,26 [-0,34; -0,18]). There was no statistically significant heterogeneity between studies (Figure 1).

HbA_{1c} level at the end of follow up

- HbA_{1c} level at the end of follow up was reported in 11 studies. Three trials (Beck 2009, Lagarde 2006 and O'Connell 2009) demonstrated superiority of CGM compared to SMBG, one superiority of SMBG, whereas the remaining studies did not reveal statistically significant differences.
- Meta-analysis of data from all trials showed that HbA_{1c} level at the end of follow up was lower in the CGM group compared to SMBG. However this difference did not reach statistical significance (WMD = -0,22 [-0,46; 0,02]), but very high heterogeneity between studies was present (I^2 = 69,06%), so this results are statistically uncertain.
- The most probable reasons for results discrepancies are differences in HbA_{1c} baseline level between the groups and small number of patients. After exclusion of two studies with the smallest number of patients (Chase 2001, Cosson 2009) the heterogeneity decreased to the acceptable level and the difference reached statistical significance in favor of CGM group (WMD = -0,31 [-0,50; -0,12]).
- Additional analysis in subgroups was performed based on the number of patients. Superiority of CGM over SMBG was demonstrated in trials with at least 50 patients (WMD = -0,31 [-0,53; -0,09]), whereas meta-analysis of studies with less than 50 patients indicated no significant difference between the groups (WMD = -0,13 [-0,59; 0,33]) (Figure 2).

Percentage of patients with target HbA_{1c}

- Four studies reported percentage of patients who achieved target HbA_{1c} level. In 3 trials (Hirsch 2008, O'Connell 2009, Tamborlane 2008) target was defined as ≤ 7% and in one study (Yates 2006) the threshold was a bit higher (≤ 7,5%). Additionally Tamborlane 2008 reported percentage of patients who achieved at least 10 % reduction in HbA_{1c} level.
- Meta-analysis of 4 trials revealed that percentage of patients who achieved treatment target was higher in patients on CGM than those on SMBG only (OR = 2.13 [1.39; 3.26]) (Figure 4).
- In one study it was shown that in CGM group significantly more patients achieved at least 10% reduction of HbA_{1c} when compared to SMBG (OR = 2,95 [1,53; 5,71]).

Hypoglycemia

- Incidence of hypoglycemic episodes was reported in 3 trials. In 2 studies (Beck 2009, Hirsch 2008) patients using CGM experienced hypoglycemic events less frequently as compared to those in SMBG group while in the third one (Lagarde 2005) the difference between groups was not statistically significant. Pooled results showed statistically significant difference between groups in favor of CGM (SMD = -0.33 [-0.56; -0.10]) (Figure 5).
- No significant differences were revealed with respect to the change in number of hypoglycemic episodes, time spent in hypoglycemia and change of time spent in hypoglycemia (Table 2).
- Risk of severe hypoglycemic episodes was comparable in both groups (8.2% vs. 9.9%; RR = 0.82 [0.47; 1.46]), as well as the risk of severe hypoglycemic incidence requiring assistance (4.4% vs. 2.7%; RR = 1.63 [0.69; 3.83]).

Hyperglycemia

- Change (from baseline) of hyperglycemia duration was reported in 3 trials.
- In 2 studies statistically significant reduction of time spent in hyperglycemia was demonstrated regardless of the definition of hyperglycemia (>180, 190, 250 mg/dl). Data presented in the third study (Beck 2009) was inappropriate to conclude about statistical significance of difference between the groups.
- No significant differences were revealed with respect to the incidence of hyperglycemia, reduction of time spent in hypoglycemia and time spent in hyperglycemia (Table 2), as well as the risk of ketoacidosis (0,8% vs. 0,4%; RR = 1,63 [0,69; 3,83]).

Safety

- Safety analysis indicated that CGM system was well tolerated by patients. Reported adverse events (AEs) included adverse reaction at the sensor implantation site, such as pain, redness, itching and system irregularities. No severe adverse events were observed.

Conclusions

- The use of CGM system in patients with T1DM may contribute to improvement of glycemic control, as measured by HbA_{1c} time spent in hyperglycemia.
- Moreover, CGM system allows to reduce the incidence of any hypoglycemic episodes, but does not influence the risk of severe hypoglycemic episodes.
- CGM system is safe and reported adverse events are only cases of uncomplicated, mild implantation-site skin reactions.

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AE	Adverse Event
AUC	Area Under Curve
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
HbA_{1c}	Glycosylated Hemoglobin
MDI	Multiple Insulin Injections
OR	Odds Ratio
RCT	Randomized Controlled Trial
SCII	Continuous Subcutaneous Insulin Infusion
SMBG	Self-Monitoring Blood Glucose
SMD	Standardized Mean Difference
T1DM	Type 1 Diabetes Mellitus
WMD	Weighed Mean Difference

Figure 1. HbA_{1c} change from baseline for the comparison between CGM and SMBG

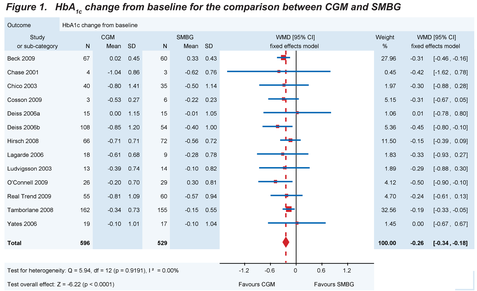

Figure 2. HbA_{1c} level at the end of follow-up for the comparison between CGM and SMBG

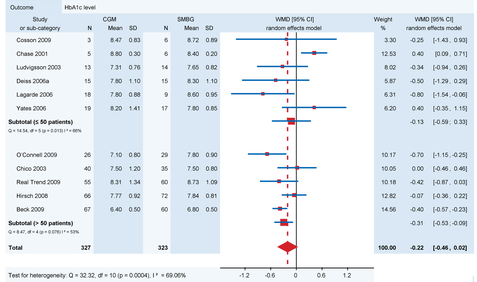

Figure 3. Odds ratio for target HbA_{1c} level for the comparison between CGM and SMBG

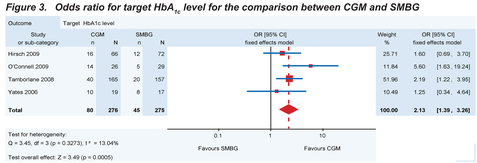

Figure 4. Standardized mean difference for the incidence of hypoglycemic episodes – comparison between CGM and SMBG

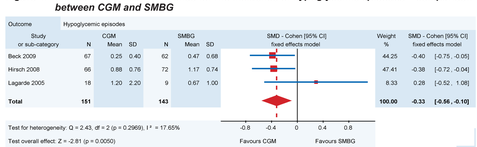

Table 1. Characteristics of RCTs included in the analysis

Study	Subgroups	No of patients	Study arm	Mean age	Baseline HbA_{1c} [%][a]	Insulin regimen
Beck 2009	Children, adolescents, adults	67	CGM[a]	29.3 (16.3)	6.4 (0.5)	CSII, MDI
		62	SMBG	32.0 (17.7)	6.5 (0.3)	
Chase 2001	Children, adolescents	5	CGM (Medtronic)	14,8 (2.2)	10.0 (0.7)	CSII, MDI
		6	SMBG	12.0 (0.6)	9.0 (1.2)	
Chico 2003	Adults	40	CGM (Medtronic)	36.5 (12)	8.3 (1.6)	MDI
		35	SMBG	41 (10)	8.0 (1.4)	
Cosson 2009	Adults	14	CGM (Menarini Diagnostics)	47.3 (7.1)	9.00 (0.67)	CSII, MDI
		20	SMBG	52.0 (12.7)	9.03 (0.12)	
Deiss 2006a	Children, adolescents	15	CGM (Medtronic)	10.3 (2–16)[d]	7.8 (1.2)	MDI
		15	SMBG	12.4 (3–16)[d]	8.4 (1.0)	
Deiss 2006b	Children, adolescents, adults	162	CGM (Medtronic)	Children: 14,4 (8,0–18,9)[d], Adults: 39,1 (19,0–59,5)[d]	9.5 (1.1)	CSII, MDI
			CGM (Medtronic)		9.6 (1.2)	
			SMBG		9.7 (1.3)	
Hirsch 2008	Children, adolescents, adults	66	CGM (Medtronicb)	33 (1.,6)	8.49 (0.8)	CSII
		72	SMBG	33.2 (16.4)	8.39 (0.64)	
Lagarde 2006	Children, adolescents	18	CGM (Medtronic)	9.9 (3.2)	8.4 (0.98)	CSII, MDI
		9	SMBG	14.2 (2.9)	8.8 (0.86)	
Ludvigsson 2003	Children, adolescents	16	CGM (Medtronic)	12.5 (3.3)	8.0 (1.1)	CSII, MDI
		16	SMBG			
O'Connell 2009	Children, adolescents, adults	31	CGM (Medtronic[b])	23.4 (8.6)	7.3 (0.6)	CSII
		31	SMBG	23.0 (8.1)	7.5 (0.7)	
Real Trend 2009	Children, adolescents, adults	55	CGM (Medtronic[c])	28.1 (15.1)	9.11 (1.28)	CSII
		60	SMBG	28.8 (16.7)	9,28 (1.19)	
Tamborlane 2008	Children, adolescents, adults	165	CGM[a]	23.8 (14.4)	7.0 – ≥9.0	CSII, MDI
		157	SMBG			
Yates 2006	Children, adolescents,	19	CGM (Medtronic)	14.7 (13.6–14.4)[d]	8.2 (0.9)	CSII, MDI
		17	SMBG	14.1 (12.8–15.3)[d]	7.9 (0.9)	

a) DexCom, Medtronic lub Abbott Diabetes Care; b) system zintegrowany z pompą insulinową; c) średnia (SD), jeżeli nie podano inaczej; d) mediana (zakres)

Table 2. Incidence and duration of hypo- and hyperglycemic episodes

Variable	Follow up	Nr of patients	Result [95% CI]	References
Incidence of hypoglycemia [episodes/day]	3–6 months	294	SMD = -0.33 [-0.56; -0.10]	1,7,8
Change in number of hypoglycemic episodes [episodes/day]	6 months	100	MD = 0.00 [-0.32; 0.32]	11
Time spent in hypoglycemia	3–6 months	265	NS	1,5,8–10
Change of time spent at hypoglycemia	6 months	342	NS	1,11–13
Incidence of hyperglycemia [episodes/day]	6 months	138	MD = 0.21 [-0.08; 0.50]	7
Change in number of hyperglycemic episodes [episodes/day]	6 months	100	MD = 0.00 [-0.28; 0.28]	11
Time spent in hyperglycemia	6 months	243	NS	1,5,9–10
Change of time spent in hyperglycemia >180 mg/dl [min./day]	6 months	322	MD = -60.52 [-101.35; -19.69]	12–13
Change of time spent in hyperglycemia >190 mg/dl [h/day]	6 months	100	MD = -2.80 [-4.52; -1.08]	11
Change of time spent in hyperglycemia >250 mg/dl [min./day]	6 months	322	MD = -29.15 [-45.37; -12.92]	12–13