Impact of rtCGM Usage on a Combined Patient Reported Outcome: A Post-hoc Analysis of the HypoDE Study

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ABSTRACT

The HypoDE study, a randomized multi-center trial, showed that rtCGM use reduces the number of low glucose events (< 55 mg/dl for at least 20 min) per 28 days significantly from 10.4 to 3.4 events compared to SMBG (13.5 to 13.2 events) in MDI-treated type 1 diabetic patients with hypoglycemia problems. We analyzed the impact of rtCGM use on patient-reported-outcomes (PRO). A combined PRO consisting of a specific measure of satisfaction with glucose monitoring (GMSS), a diabetes-specific assessment (DDS) and a generic measure (EQ-5D) was used.

In a factor analysis, all three scales loaded on one factor. AI questionnaire scores were z-transformed as well as the number of low glucose events. The figure shows the effect sizes of the combined PRO and the single scores as well as of the low glucose events. There was a significant positive impact of rtCGM use on the combined PRO. However, only GMSS but not DDS or EQ-5D showed a significant impact. The more device-specific the PRO, the higher was the effect size. Interestingly, the impact of rtCGM use on biochemical hypoglycemia had a remarkably larger effect size than the combined PRO. Since most other rtCGM studies are powered to detect a benefit in glycemic endpoints and in PRO, the lower impact of rtCGM on PRO is a barrier to prove the efficacy of rtCGM on PRO like quality of life, diabetes distress or satisfaction with treatment.

BACKGROUND

The HypoDE study was a randomized controlled trial in people with diabetes and multiple daily insulin injections and hypoglycemia problems. It could be demonstrated that rtCGM was able to significantly reduce the number of low glucose events (glucose < 55 mg/dl for at least 20 minutes) compared to a control group performing blood glucose (SMBG) measurements (10.4 to 3.4 events vs. 13.5 to 13.2 events per 28 days).

Also, patient-reported-outcomes (PRO) were assessed in the HypoDE study. This analysis evaluated the impact of rtCGM on these PRO measures as well as on a combined PRO outcome.

METHODS

A combined outcome was calculated consisting of different PRO measures:

- Glucose-monitoring-specific: Satisfaction with the glucose-monitoring device (Glucose Monitoring Satisfaction Survey: GMSS)
- Hypoglycemia-specific: Fear of hypoglycemia (Hypoglycemia Fear Survey: HFS)
- Diabetes-specific: Diabetes distress (Diabetes Distress Scale for type 1 diabetes: T1-DDS)
- Generic: Health-related quality of life (EQ-5D)

A factor analysis confirmed that all scales loaded on a single factor; hence, justifying the combination to a single score. In order to calculate the combined outcome, all scales were z-transformed.

The effect sizes (*d*) of the single PRO scales, the combined PRO outcome and the primary outcome of the HypoDE study (low glucose events) were compared.

RESULTS

Sample characteristics are shown in Table 1. There were no significant differences between the control and rtCGM-group.

Glucose-monitoring-specific (Figure 1):

- There was a significant difference for the overall satisfaction with the glucose-monitoring device between participants with and without rtCGM (*d* = 0.38).
- Using rtCGM was associated with a higher openness/flexibility and less behavioral burden compared to SMBG.

Hypoglycemia-specific (Figure 2):

- While participants with rtCGM consistently showed lower scores on the Hypoglycemia Fear Survey, these differences failed to reach statistical significance. The overall effect size was small (*d* = 0.23).

Diabetes-specific (Figure 3):

- Overall diabetes distress was not significantly different between the two groups (*d* = 0.12).
- However, using rtCGM was associated with less hypoglycemia-related distress.

Generic and combined outcome (Figure 4):

- There was no effect of rtCGM on health-realted quality of life (*d* = 0.18).
- rtCGM had a significant effect on the combined PRO outcome and led to a higher/more favourable combined score.

Comparison of effect sizes (Figure 5):

- While rtCGM had a large effect on the primary outcome (*d* = 0.92), there were only small effects on PRO-measures and the combined PRO outcome (*d* = 0.24).
- The most specific PRO "satisfaction with the glucose monitoring device" achieved the highest effect size.

CONCLUSIONS

There was a huge difference between the effect sizes for the glycemic outcome and the PRO-outcomes. Furthermore, within the different PRO measures, there was some variation in effect size with the largest effect for more specific measures.

Usually, studies on rtCGM are powered for a glycemic primary endpoint. With the much smaller effect sizes of PRO measures, therefore, it is difficult to demonstrate significant effects of rtCGM on other outcomes such as diabetes distress or quality of life.

When interpreting the effects of rtCGM on such PRO outcomes, it should be taken into account that most clinical rtCGM studies are not powered to detect differences in PRO measures.

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Table 1: Sample Characteristics

	Control group (n = 74)	rtCGM (n = 75)
Demographic and medical characteristics		
Age in years, *M (SD)*	47.3 (11.7)	45.8 (12.0)
Female gender, *n (%)*	25 (33.8)	35 (46.7)
Body Mass Index in kg/m², *M (SD)*	26.0 (4.6)	26.1 (6.7)
Diabetes duration in years, *M (SD)*	21.6 (13.9)	20.9 (14.0)
A1c (central lab), in %, *M (SD)* / in mmol/mol, *M (SD)*	7.3 (1.0) / 56.7 (10.6)	7.6 (1.0) / 59.3 (10.9)
Treatment characteristics		
Basal insulin analogue, *n (%)*	73 (98.6)	71 (94.7)
>1 basal insulin injections per day, *n (%)*	47 (64.4)	39 (52.0)
Basal insulin daily dose in IU, *M (SD)*	20.1 (10.8)	23.9 (16.2)
Bolus insulin analogue, *n (%)*	66 (89.2)	67 (90.5)
Bolus insulin daily dose in IU, *M (SD)* (based on n=127)	24.3 (12.2)	26.8 (29.5)
Hypoglycemia problems		
Severe hypoglycemia in the past 12 months, *n (%)*	45 (60.8)	47 (62.7)
Hypoglycemia unawareness (hypoglycemia unawareness score ≥4), *n (%)*	68 (91.9)	71 (94.7)
Hypoglycemia unawareness score, *M (SD)*	4.7 (1.3)	5.0 (1.1)

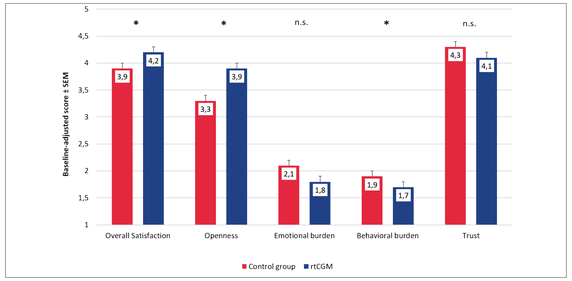

Figure 1: Differences in satisfaction with glucose monitoring device (GMSS) between participants with and without rtCGM use. * p < .05

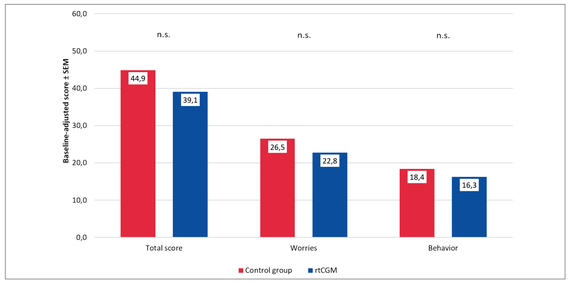

Figure 2: Differences in fear of hypoglycemia (HFS) between participants with and without rtCGM use. * p < .05

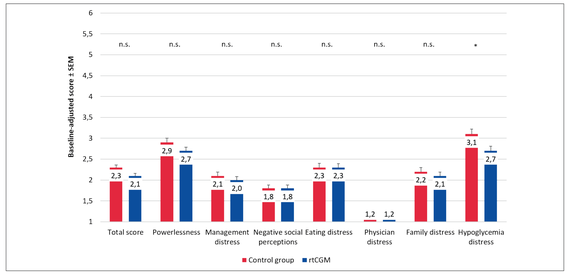

Figure 3: Differences in diabetes distress (DDS) between participants with and without rtCGM use. * p < .05

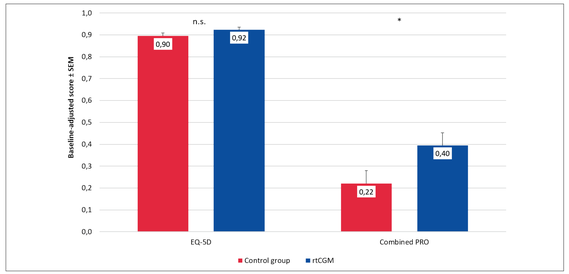

Figure 4: Differences in health-related quality of life (EQ-5D) and the combined PRO between participants with and without rtCGM use. * p < .05

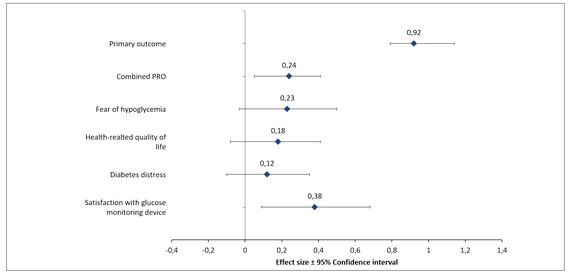

Figure 5: Effect sizes of difference between participants with and without rtCGM use for the different PRO-measures, the combined PRO and the primary outcome

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