Lower Daily Carbohydrate Intake Is Associated With Improved Glycemic Control in Adults With Type 1 Diabetes Using a Hybrid Closed-Loop System

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OBJECTIVE

To assess the association between daily carbohydrate (CHO) intake and glycemic control in adult hybrid closed-loop (HCL) users with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

Mean individual daily CHO intake (MIDC) and relative deviation from MIDC (≤80% low, 81–120% medium, >120% high CHO consumption) were compared with parameters of glycemic control assessed by continuous glucose monitoring.

RESULTS

Records from 36 patients (26 male, 10 female; age 36.9 ± 13.5 years; HbA_{1c} 7.1 ± 0.9% [54 ± 10 mmol/mol]) provided 810 days of data (22.5 ± 6.7 days per patient). Time in range (70–180 mg/dL) for low, medium, and high CHO consumption was 77.4 ± 15.4%, 75.2 ± 16.7%, and 70.4 ± 17.8%, respectively ($P < 0.001$). Time above range (>180 mg/dL) was 20.1 ± 14.7%, 22.0 ± 16.9%, and 27.2 ± 18.4%, respectively ($P < 0.001$). There was no between-group difference for time in hypoglycemia (<70 mg/dL; $P = 0.50$).

CONCLUSIONS

Daily CHO intake was inversely associated with glycemic control in adults with T1D using an HCL system. Lower CHO intake may be a strategy to optimize glucose control in HCL users.

Hybrid closed-loop (HCL) therapy improves overall glucose control in patients with type 1 diabetes (T1D) (1,2). Whether reduced carbohydrate (CHO) intake has an additional beneficial effect on diabetes control in HCL users is unknown. The current study quantified the association of glycemic control and daily CHO intake in individuals with T1D using an HCL system. We hypothesized that a lower daily CHO intake is associated with improved diabetes control.

RESEARCH DESIGN AND METHODS

This was a retrospective, single-center study approved by the local ethics committee. All included patients provided informed consent. We included patients treated with the MiniMed 670G (MM670G; Medtronic, Northridge, CA) between November 2018 and February 2020 at our tertiary referral center. As part of the HCL instruction,

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patients underwent nutritional coaching according to established guidelines (3). Inclusion criteria were as follows: age ≥18 years, confirmed diagnosis of T1D, and permanent use of the MM670G system for at least 45 days prior to analysis. Clinical data were obtained from electronic medical records. For each patient, continuous glucose monitoring (CGM) data and estimated CHO values (g/day, entered by the user) were evaluated during a 30-day period before a routine visit. Only days with ≥70% available CGM data, as recommended by the 2019 consensus guidelines (4), and with time in automatic mode ≥50% were included in the analysis. CHO and CGM records of eligible days were exported with the proprietary manufacturer's software.

Mean individual daily CHO intake (MIDC, g/day) as well as the relative deviation from MIDC (rMIDC, %MIDC) were assessed to account for the interindividual differences in daily CHO intake. On the basis of rMIDC, a stratification into low (≤80%), medium (81–120%), and high (>120%) CHO consumption days was performed. Glucose control was assessed using standard CGM metrics including time in range (TIR) (70–180 mg/dL), time above range (TAR) (>180 mg/dL), time below range (TBR) (<70 mg/dL), mean glucose (mg/dL), and coefficient of variation (%) for each day (4).

All statistical analyses were performed using Stata 16.1 (StataCorp LLC, College Station, TX). Results are expressed as mean ± SD unless otherwise specified. A two-sided α-level of 5% was defined as statistically significant. The three rMIDC groups were compared using ANOVA, applying a Bonferroni correction to control for multiple comparisons in the post hoc analysis. Associations between CHO intake and CGM metrics were assessed using mixed linear models with a random effect attributed to individuals and adjusted for time in automatic mode.

RESULTS

There were 810 days of data (22.5 ± 6.7 days/patient) from 36 adults with T1D (26 male, 10 female; age 36.9 ± 13.5 years; HbA_{1c} 7.1 ± 0.9% [54 ± 10 mmol/mol]; diabetes duration 23.0 ± 13.0 years; BMI 26.5 ± 3.6 kg/m^2). Mean total daily insulin dose was 50.5 ± 19.7 IU/day (25/36 patients with ultra-rapid-acting insulin aspart, 7/36 with insulin aspart, and 4/36 with insulin lispro).

Patients used the HCL system for 107 ± 36 days before time of inclusion. Mean time of sensor use during the analysis period was 96.1 ± 6.2% and mean time in automatic mode was 91.0 ± 12.4%. Mean daily CHO intake was 166.4 ± 69.6 g distributed over 5.7 ± 3.2 meals per day. Daily CHO intake for the low, medium, and high rMIDC groups were 100.9 ± 43.3, 171.2 ± 53.4, and 222.7 ± 70.6 g/day, respectively ($P <$ 0.001). TIRs for the low, medium, and high rMIDC groups were 77.4 ± 15.4%, 75.2 ± 16.7%, and 70.4 ± 17.8%, respectively ($P < 0.001$), and TARs were 20.1 ± 14.7%, 22.0 ± 16.9%, and 27.2 ± 18.4%, respectively ($P < 0.001$). There was no significant difference for TBR ($P = 0.50$).

Table 1 shows daily CHO intake, total daily insulin dose, and CGM metrics according to rMIDC, stratified by time in automatic mode. In patients using the automatic mode <80%, there was no difference across CHO groups. In individuals spending >90% of the day in automatic mode, lower CHO intake was associated with improved CGM parameters (except for TBR). Supplementary Figure 1 depicts the association of daily CHO intake and TIR in each individual. On average, a 10% increase in daily CHO intake was associated with a decrease of 1.1% in TIR and a 1.2% increase in TAR ($P < 0.001$ for both analyses). There was no effect of daily CHO intake on TBR ($P = 0.42$).

CONCLUSIONS

The main findings of this study are twofold. First, daily CHO intake was inversely associated with glycemic control in adult people with T1D using an HCL system. Second, this effect was more pronounced in patients with higher use of automatic mode.

To the best of our knowledge, this is the first systematic analysis of the association between CHO intake and glycemic control in patients with T1D using HCL. Ranjan et al. (5) reported that in 10 individuals with T1D using sensor-augmented pump therapy, TIR significantly improved by 11% during 1 week of a very low CHO diet (≤50 g/day) compared with a high CHO diet (≥250 g/day). Of note, the difference in CHO intake per day was far more pronounced in the study by Ranjan et al. when compared with our setting. Still, the 10% greater relative TIR we report in the lower CHO group suggests that a more moderate CHO reduction may be sufficient and equally effective when using HCL. A recent 12-week crossover intervention with low-CHO (<100 g/day) vs. high-CHO diet (≥250 g/day) under sensor-augmented pump therapy showed no effect on TIR but did show lower TBR and glucose variability in the low CHO group (6). While we did not detect an association of CHO intake with TBR in our study, we found a lower glycemic variability with reduced CHO intake, particularly in patients using automatic mode >90% of the time. In a recent 12-week study evaluating the effects of 100 vs. 200 g/day of CHO in 10 individuals with T1D on multiple daily injections, HbA_{1c} was lower in the CHO-restricted group, but TIR was not reported (7). However, an increase in TIR of 10% corresponds to a decrease in HbA_{1c} of ~0.5% (5.0 mmol/mol) (4), thereby rendering their findings compatible to the present analysis.

Our results imply that even in the era of HCL therapy, lifestyle factors, such as diet (in particular CHO meal composition), still play an important role in achieving optimal glycemic control. This is further emphasized by the fact that the observed effect was strongest in patients using automatic mode most frequently. Previous studies have shown that in the postprandial phase, CHO is the primary determinant of glucose excursions (8,9), thereby strongly affecting time spent inside or outside of the target range (10). In line with this, our findings suggest that the current HCL algorithms are particularly challenged by higher CHO amounts. This is consistent with studies reporting improved glucose control during nighttime in HCL (1,11), mainly due to a reduction of additional external factors, such as CHO intake. We cannot exclude that patients, while in automatic mode, may have entered phantom CHO to correct hyperglycemia. However, the CHO entries in the different automatic mode groups did not differ, speaking strongly against a relevant interference of phantom CHO in the present analysis.

We fully acknowledge a number of limitations in our analysis. First, the retrospective and single-center design does not allow for exclusion of selection bias or other systematic errors. The study

Table 1—CHO intake, insulin dose, and CGM metrics based on the rMIDC groups and time spent in automatic mode

	≤80% (days = 180)	81–120% (days = 460)	>120% (days = 170)	*P* value
CHO (g/day)	100.9 ± 43.3	171.2 ± 53.4***	222.7 ± 70.6***	<0.001
Automatic mode <80%	103.0 ± 41.1	175.0 ± 51.6***	236.3 ± 76.2***	<0.001
Automatic mode 80–90%	104.5 ± 41.3	172.8 ± 51.0***	239.5 ± 81.8***	<0.001
Automatic mode >90%	99.1 ± 44.0	170.0 ± 54.4***	216.7 ± 66.9***	<0.001
TDD (IU/day)	45.0 ± 16.2	49.6 ± 18.8*	59.1 ± 22.8***	<0.001
Automatic mode <80%	49.2 ± 16.1	51.4 ± 17.4	61.5 ± 16.8**	0.011
Automatic mode 80–90%	48.3 ± 18.9	51.7 ± 16.8	72.9 ± 32.3***	<0.001
Automatic mode >90%	42.4 ± 15.0	48.6 ± 19.5**	56.1 ± 21.1***	<0.001
TIR (70–180 mg/dL)	77.4 ± 15.4	75.2 ± 16.7	70.4 ± 17.8***	<0.001
Automatic mode <80%	68.9 ± 17.7	67.1 ± 20.4	67.7 ± 18.2	0.88
Automatic mode 80–90%	71.5 ± 16.4	69.7 ± 19.3	55.3 ± 17.2**	0.003
Automatic mode >90%	82.4 ± 11.8	78.3 ± 14.1*	73.8 ± 16.3***	<0.001
TAR (>180 mg/dL)	20.1 ± 14.7	22.0 ± 16.9	27.2 ± 18.4***	<0.001
Automatic mode <80%	27.0 ± 17.9	29.3 ± 21.0	28.8 ± 19.4	0.83
Automatic mode 80–90%	24.8 ± 15.5	27.0 ± 20.4	42.2 ± 19.0**	0.002
Automatic mode >90%	16.2 ± 11.5	19.2 ± 14.1	24.2 ± 16 8***	<0.001
TBR (<70 mg/dL)	2.4 ± 4.5	2.8 ± 4.9	2.3 ± 3.5	0.50
Automatic mode <80%	4.1 ± 5.0	3.5 ± 5.1	3.5 ± 4.2	0.81
Automatic mode 80–90%	3.7 ± 6.9	3.2 ± 5.6	2.5 ± 4.0	0.77
Automatic mode >90%	1.4 ± 2.9	2.5 ± 4.8	2.1 ± 3.2	0.06
Mean glucose (mg/dL)	146.3 ± 19.8	147.3 ± 22.3	155.1 ± 25.6***	<0.001
Automatic mode <80%	154.6 ± 27.7	154.6 ± 27.9	159.0 ± 30.6	0.77
Automatic mode 80–90%	150.4 ± 20.8	154.2 ± 28.6	174.1 ± 29.2**	0.005
Automatic mode >90%	141.8 ± 13.8	144.2 ± 18.2	150.9 ± 20.4***	<0.001
CV glucose (%)	29.3 ± 10.4	29.1 ± 7.7	30.7 ± 8.4	0.09
Automatic mode <80%	36.3 ± 14.6	31.7 ± 8.2	34.6 ± 8.6	0.07
Automatic mode 80–90%	31.9 ± 9.9	30.8 ± 8.8	34.6 ± 9.9	0.24
Automatic mode >90%	25.9 ± 6.3	28.1 ± 7.1*	29.2 ± 7.6**	0.001

Asterisks denote significance levels of postestimations comparing the rMIDC group ≤80% against the rMIDC group 81–120%, and against the rMIDC group >120%: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. CV, coefficient of variation; TDD, total daily dose.

covers a limited time period, and evaluation of the effect over a longer term is needed. Second, the data do not allow for a statement on the type of CHO consumed, while CHO quality (e.g., glycemic index) and other macronutrients (fats and proteins) may influence glucose dynamics (12). Third, documented CHO intake may be biased since our analysis is based on CHO values that were estimated by the HCL users (and not a dietitian). Inaccurate CHO counting is frequent and mean errors of 20% have been reported (13); however, they are likely to be balanced within individuals. Finally, this study is based on data from patients of mainly Caucasian ethnicity with male preponderance, limiting generalization to other populations.

In conclusion, the present analysis provides evidence that lifestyle factors, such as lower CHO intake, play an important role in achieving optimal glycemic control in adults with T1D using an HCL system. The effect appears more pronounced with higher use of automatic mode, suggesting that lower CHO intake may facilitate glucose control particularly in patients consistently using the HCL algorithm.

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References

1. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 2017;19:155–163
2. Brown SA, Kovatchev BP, Raghinaru D, et al.; iDCL Trial Research Group. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. N Engl J Med 2019;381:1707–1717
3. American Diabetes Association. 4. Lifestyle management: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S38–S50
4. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603
5. Ranjan A, Schmidt S, Damm-Frydenberg C, Holst JJ, Madsbad S, Nørgaard K. Short-term effects of a low carbohydrate diet on glycaemic variables and cardiovascular risk markers in patients with type 1 diabetes: a randomized open-label crossover trial. Diabetes Obes Metab 2017;19:1479–1484
6. Schmidt S, Christensen MB, Serifovski N, et al. Low versus high carbohydrate diet in type 1 diabetes: a 12-week randomized open-label crossover study. Diabetes Obes Metab 2019;21:1680–1688
7. Krebs JD, Parry Strong A, Cresswell P, Reynolds AN, Hanna A, Haeusler S. A randomised trial of the feasibility of a low carbohydrate diet vs standard carbohydrate counting in adults with type 1 diabetes taking body weight into account. Asia Pac J Clin Nutr 2016;25:78–84

8. Scavone G, Manto A, Pitocco D, et al. Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in type 1 diabetic subjects: a pilot study. Diabet Med 2010;27:477–479
9. Rabasa-Lhoret R, Garon J, Langelier H, Poisson D, Chiasson JL. Effects of meal carbohydrate content on insulin requirements in type 1 diabetic patients treated intensively with the basal-bolus (ultralente-regular) insulin regimen. Diabetes Care 1999;22:667–673
10. Thabit H, Hovorka R. Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia 2016;59:1795–1805
11. Leelarathna L, Dellweg S, Mader JK, et al.; AP@home Consortium. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. Diabetes Care 2014;37:1931–1937
12. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpert HA. Impact of fat, protein, and glycemic index on postprandial glucose control in type 1 diabetes: implications for intensive diabetes management in the continuous glucose monitoring era. Diabetes Care 2015;38:1008–1015
13. Brazeau AS, Mircescu H, Desjardins K, et al. Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. Diabetes Res Clin Pract 2013;99:19–23