Missed Insulin Boluses for Snacks in Youth with Type 1 Diabetes

Running Title: Missed Insulin Boluses for Snacks

Brandon W. VanderWel, BA, University of Colorado
Laurel H. Messer, MPH, RN, CDE, University of Colorado
Lauren A. Horton, BA, University of Colorado
Bryan McNair, BA, University of Colorado
Erin C. Cobry, BS, University of Colorado
Kim K. McFann, PhD, University of Colorado
H. Peter Chase, MD, University of Colorado

Corresponding Author:
H. Peter Chase, MD:
Email: peter.chase@ucdenver.edu

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**Objective:** To evaluate the effects of missed insulin boluses for snacks in youth with type 1 diabetes.

**Research Design and Methods:** Three months of simultaneous continuous subcutaneous insulin infusion and continuous glucose monitoring data from 9 subjects were retrospectively evaluated. Glucose excursions between 1330-1700 hrs were defined as relating to snacks with insulin or snacks with no insulin administered. Area under the curve >180 mg/dl (AUC>180), average Δ glucose and rate of change (ROC) were analyzed and compared within and between groups.

**Results:** A total of 94 snacks without insulin and 101 snacks with insulin were analyzed. Snacks without insulin had significantly higher log (AUC>180+1) (1.26 vs. 0.44 mg/dL-event; p<0.001), Δ glucose (114 vs. 52 mg/dL; p<0.001) and average ROC (1.3 vs. 1.1 mg/dL-min; p<0.001).

**Conclusion:** This study shows that afternoon snacks without insulin boluses are common and result in significantly higher glucose excursions compared to snacks with insulin administration.
Previous studies have demonstrated the deleterious effect of missed insulin doses for meals. (1-4) None, however, have examined the effect of missed insulin boluses for snacks. Because youth frequently snack when unsupervised, it is likely that missed insulin boluses are even more common for snacks than for meals. The purpose of this investigation was to use data from continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) together to evaluate the glycemic profiles of missed insulin boluses for afternoon snacks.

**RESEARCH DESIGN AND METHODS**

This is a retrospective (Institutional Review Board approved) analysis of 810 days of CSII and CGM data from 9 youth with diabetes. All subjects used the Minimed Paradigm® REAL Time System (Northridge, CA) for insulin delivery and CGM. Reports were downloaded using Medtronic CareLink® software. Afternoon snacks were identified on CGM as glucose excursions beginning between 1330-1700 hours. A glucose excursion was considered resolved when glucose levels remained steady for ≥15 minutes. Glucose excursions with incomplete CGM data or CSII suspension >15 min were discarded. Glucose excursions were identified as a snack with no insulin (SNI) or a snack with insulin (SWI) as described below, and possible snacks not fitting these criteria were excluded from analysis.

SNI criteria were: 1) no bolus administered within ±30 min of the beginning of the glucose excursion 2) increase in glucose level ≥50 mg/dL 3) average rate of change (ROC) from baseline to peak of excursion ≥0.8 mg/dL/min 4) starting glucose level >80 mg/dL (to exclude treatment of hypoglycemia) and 5) determined not to be the dinner meal. Carbohydrate contents for snacks are not known for SNI.

SWI criteria were: 1) bolus administered within ±30 min of the beginning of the glucose excursion 2) determined not to be the dinner meal 3) determined not to be an exclusive correction bolus (confirmed on pump download).

Each glucose excursion was characterized by baseline glucose level, peak glucose level, end glucose level, duration of excursion, time spent >180 mg/dL, area under the curve >180 mg/dl (AUC>180), total amplitude of excursion (Δ glucose), average ROC, and insulin administered. The study’s primary outcome was the comparison between the AUC>180 of the glucose excursions for SNI and SWI. Secondary outcomes included comparing the average ROC and Δ glucose for SNI and SWI.

All statistical analysis used Bonferroni adjusted p values for multiple comparisons. Results are expressed as mean ±1 SD. Exploratory analyses revealed positive skew in the outcome variables (AUC>180, Δ glucose and ROC). Since AUC>180 was used, this resulted in a zero inflated distribution, thus a two-stage model was employed. Generalized Estimating Equations were used to determine the distribution of events with BG ≤180 versus BG > 180 between SNI and SWI. Mixed models were applied by regressing log(AUC>180 + 1.0), log(Δ glucose) and log(ROC), on to SNI/SWI (unbolused or bolused snack) adjusting for age, gender, and repeated measures on subjects. Results are presented as mean or geometric mean and 95% CI. A general linear mixed
model approach suggested by Cnaan et al.\(^8\) was used to model Blood Glucose curves.

RESULTS

Data from 9 subjects (5 female) with a mean hemoglobin A1c of 7.6 ± 0.7%, mean duration of diabetes of 8.6 ± 6.3 yrs and a mean age of 15.1 ± 8.8 yrs were analyzed. Of 195 glucose excursions identified, 94 were classified as SNI and 101 as SWI. Baseline glucose values between SNI and SWI were not significantly different (p=1.0). 76 of 94 (81.7%) SNI resulted in BG > 180 compared to 51 of 101 (50.5%) for a resulting OR = 4.80 (2.46-9.40), p < 0.0001 after adjusting for age, gender and repeated measures among subjects. Mean time spent above 180 mg/dL was 105 ± 89 minutes for SNI and 34 ± 42 minutes for SWI. The average glucose excursion for SNI began at 124 ± 47 mg/dL, peaked at 252 ± 65 mg/dL after 100 ± 58 minutes and resolved after 175 ± 97 min at 157 ± 59 mg/dL. The average glucose excursion for SWI began at 130 ± 51 mg/dL, peaked at 191 ± 55 mg/dL after 53 ± 27 minutes and resolved after 98 ± 48 minutes at 145 ± 49 mg/dL. Both the main effects of time and SNI versus SWI were significant (p>0.0001) as well as the second order effects and interactions concluding that the two curves were significantly different (p<0.001). A table of the ratio of covariate effects and confidence intervals is included in the Appendix which is available at http://care.diabetesjournals.org.

Glucose excursions from SNI had a mean log (AUC>180 + 1) of 1.26 (95% CI: 1.06, 1.46) compared to 0.44 mg/dL-event (95% CI: 0.31, 0.57) for SWI (p<0.001). Neither age nor gender had a significant effect on AUC>180 (p=1.0 and p=0.50, respectively).

The Δ glucose adjusted mean for SNI (114 mg/dL [101,129]) was significantly different (p<0.001) from SWI (52 mg/dL [47, 59]). Age was not found to have an effect (p=0.08).

The average ROC was significantly different (p<0.005) between SNI (1.3 [95% CI: 1.2, 1.5]) and SWI (1.1 mg/dl/min [95% CI: 1.0, 1.2]). Neither age nor gender significantly affected the ROC (p=1.0 for both).

CONCLUSIONS

This study shows that when insulin is omitted for afternoon snacks, the area under the curve (>180 mg/dl) is twice that of excursions for bolused snacks. Furthermore, SNI excursions demonstrated a steeper increase in glucose levels and twice the amplitude of SWI excursions. In this study, approximately 50% of boluses for snacks (94 of 195) were missed.

Diabetes care providers often put much emphasis on mealtime insulin boluses but fail to focus on snacks. Since snacking involves smaller amounts of food over a longer period of time when compared to meals, the glycemic profiles are different. Future prospective studies should include many more subjects, as well as data relating to insulin reduction and food intake with exercise, to further characterize these excursions. Overall, missed insulin boluses for snacks contribute to significant hyperglycemia. Diabetes care providers need to stress the importance of bolusing for snacks as well as for meals.

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REFERENCES

Figure Legend:
A comparison of glucose excursions for snacks with insulin (dashed line) and snacks without insulin (solid line).

Figure: Comparison of glucose excursions