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Insulin-on-board limitation through continuous action on glucose target improves postprandial glycaemia in type 1 diabetes

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Abstract

Background: Postprandial (PP) control remains a challenge for closed-loop (CL) systems. Few studies with inconsistent results have systematically investigated the PP period.

Objective: To compare a new CL algorithm with current pump therapy (OL) in the PP glucose control in type 1 diabetes (T1D) subjects.

Methods: A crossover-randomized study was performed in two centers. 20 T1D subjects (F/M 13/7, disease duration 22.6±9.9 years, A1c 7.8±0.7%) underwent an 8-hour mixed meal test on 4 occasions. On two (CL1/CL2), after meal-announcement a bolus was given followed by an algorithm-driven basal infusion based on continuous glucose monitoring (CGM). Alternatively, in OL1/OL2 conventional pump therapy was used. Main Outcome Measures were: Glucose variability, estimated with the coefficient of variation (CV) of the area-under-the-curve (AUC) of plasma glucose (PG) and CGM values and from the analysis of the glucose-time series; mean, maximum (C_{max}) and time to C_{max} glucose concentrations and time in range (<70, 70-180, >180 mg/dl).

Results: CVs of the glucose AUCs were low and similar in all studies (around 10%). However, CL achieved greater reproducibility and better PG control in the PP period: CL1=CL2<OL1<OL2 (PG_{mean} 123±47 and 125±44 vs. 152±53 and 159±54mg/dl). Cmax OL 217.1±67.0 vs. CL 183.3±63.9mg/dl, $p<0.0001$. Time-in-range was higher with CL vs. OL (80 vs. 64%; $p<0.001$). Neither the time-below 70 mg/dl (CL 6.1 vs. OL 3.2%; $p>0.05$) nor the need for oral glucose were significantly different (CL 40.0% vs. OL 22.5% of meals; $p=0.054$).

Conclusions: This novel CL algorithm effectively and consistently controls PP glucose excursions without increasing hypoglycemia.

Introduction

Postprandial (PP) glucose fluctuations are one of the main contributors to chronic hyperglycemia and glucose variability in subjects with type 1 diabetes (T1D). Additionally, the poor reproducibility of PP glucose response is burdensome not only for patients but also for healthcare professionals using and prescribing intensive insulin therapy. Automated closed loop (CL) glucose control systems are expected to improve PP hyperglycemia and variability. However, meal-induced glucose perturbations and PP hyperglycemia compensation strategies remain one of the most difficult challenges for CL systems in the management of T1D.

Until now, different approaches have been suggested to counteract meal-induced disturbances in CL studies. Fully automated CL control without prior information regarding meal size and insulin delivery optimization have shown lower performance during the PP period either in single- or in dual-hormone CL systems (1-3). Other less-ambitious approaches in which meals are announced to the system (meal announcement, semi closed-loop) giving full prandial bolus (4,5), or at least a percentage (priming boluses), leaving the rest to the CL controller (6) have been evaluated. More recently, other strategies alternative to continuous subcutaneous insulin infusion (CSII) such as the addition of pramlintide, liraglutide or technosphere inhaled insulin have been shown to improve PP glucose excursions (7,8). However, these strategies do not relieve the burden of decision-making before meals and/or add complexity to the CL therapy. For these reasons, meal announcement appears to be the easiest way to improve PP glucose control in CL systems.

Despite the use of meal announcement, the main challenge of control algorithms is to find a balance between PP glucose control and hypoglycemic risk, avoiding the overcorrection of hyperglycemia. An aggressive tuning for a lower PP glucose peak may cause insulin stacking producing late hypoglycemia. Several groups have incorporated safety strategies in their algorithms such as the inclusion of constraints on residual insulin activity (insulin on-board, IOB) (9), the addition of insulin feedback (10), or inclusion of glucagon as a counterregulatory control action (bi-hormonal CL control) (11,12), with some improvement during the PP period.

An alternative proposed strategy may be using sliding mode reference conditioning (SMRC). This is a safety loop, which needs to be added to the main control loop and is only active when IOB is going to overcome any previously defined constraint (13). However, to date only an in-silico validation of this strategy is available.

Recent at-home artificial pancreas (AP) studies have demonstrated improved daytime glucose control and less within-day and between days glycemic variability as compared to pump therapy. However, the reduction of glycemic variability was mainly due to a diminution in nocturnal glycemic variability (5,14). In addition, the PP period was not systematically addressed in these studies. Hence, the superiority of CL vs. open-loop (OL) during the PP period needs still to be proven.

In this context, our study aimed to assess whether a SMRC-based CL controller is able to safely improve PP glycemic control in comparison with standard OL therapy based on CSII in subjects with type T1D.

Research Design and Methods

Study design and subjects

This was a randomized, prospective, one-way, repeated measures (four periods, two sequences) crossover study in subjects with T1D under CSII. The protocol was approved by the Ethics Committees of the Clinic University Hospital of Valencia and the Clinic University Hospital of Barcelona (clinical settings). The study was designed as an in-hospital approach fulfilling the regulatory conditions that applied in our country to this sort of projects before moving to at-home settings.

Subjects were eligible to participate if they were between 18 and 60 years of age, had a diagnosis of T1D for at least 1 year, HbA1c between 6.0-8.5% and were on CSII for at least 6 months. Hypoglycemia unawareness was ruled out using a validated questionnaire (15).

Each subject underwent an in-hospital 8-hour standardized mixed meal test (60g carbohydrate, CH) on 4 occasions. On 2 occasions (CL1 and CL2), after a meal-announcement an augmented bolus was given, followed by manual adjustments of the basal rate every 15 minutes according to a closed loop controller. On the other two occasions (OL1 and OL2) conventional CSII was used and boluses were based on the individual insulin/carbohydrates (I:CHO) ratios. All subjects were randomly assigned to sequence 1 (OL1-CL1-OL2-CL2) or 2 (CL1-OL1-CL2-OL2) with a wash-out period of at least 1 week between studies.

Patients were instructed to wear a continuous glucose monitor (CGM) device and follow a structured self-monitoring blood glucose (SMBG) protocol during a six-day period prior to the first meal test. Data from CGM and SMBG were used to obtain an individual estimated insulin sensitivity and a pharmacokinetic/pharmacodynamic model resulting in the calculation of the following parameters: I: CHO ratio, sensitivity factor, basal insulin needs, and insulin on board (IOB). These parameters were used to optimize the overall home blood glucose control (16,17) (OL) and also for the controller tuning (CL).

Study devices

CSII was carried out with the Paradigm Veo® insulin pump (Medtronic MiniMed, Northridge, CA) and CGM using Enlite-2 sensors® (Medtronic MiniMed, Northridge, CA). Two CGM were inserted at least 24h before the meal tests, to improve performance and avoid missing data and problems related to sensor drift. For safety and regulatory reasons two sensors were used in this phase of development to ensure the algorithm to be fed with the secondary CGM in case of sensor failure. In all subjects, calibration of CGM was performed using the Contour® Next Link (Ascensia Diabetes Care Holdings AG, Basel, Switzerland. Formerly Bayer). Glucose concentrations were also measured every 15 minutes with a reference method YSI 2300 Stat Plus Glucose Analyzer (YSI 2300, YSI Incorporated Life Sciences, Yellow Springs, Ohio, USA).

136 The CL system was based on a novel SMRC glucose controller (13) built in a PC. Glucose
137 values from the two CGM devices were introduced manually every 15 minutes into the
138 controller interface. Manual operation greatly simplified regulatory approval of the system in
139 the first submission of this type in Spain. However, this was not in detriment of unreasonably
140 higher sampling periods. Remark for instance that the Florence system from Cambridge
141 University, with extensive validation in inpatient and outpatient settings, uses 12 minutes as
142 sampling period, compared to 15 minutes in our case [XX] The system defined a primary and a
143 secondary CGM device automatically, based on an accuracy analysis (Absolut Relative
144 Difference –ARD– from reference) prior to the start of the CL controller. Only data from the
145 primary CGM were used except in case of malfunction, resulting in automatic switch to the
146 secondary CGM. Malfunction was defined as an ARD between the CGM reading and the PG
147 reference greater than 40% at one time point or ARD greater than 30% in two consecutive
148 periods. The insulin infusion rate for the next 15-minute time interval was calculated by the
149 controller and manually set by the attending physician/nurse.

150 The glucose controller consists in a feed-forward action plus two control loops:

151 (a) The feed-forward action is an augmented bolus calculated based on meal announcement. The
152 value of the bolus is the result of adding to the standard bolus the amount of basal insulin that
153 would be delivered in the next hour in the case of being in open loop.

154 (b) The inner control loop is a PID-type controller designed to drive the measured glucose to a
155 target value. It is tuned from the insulin pump settings.

156 (c) The outer control loop is based on SMRC and modulates the glucose target value on the
157 estimated IOB minimizing the impact of controller over-correction resulting in late
158 hypoglycemia. When the estimated IOB is beyond pre-specified limits a high-frequency
159 discontinuous signal is generated and filtered inducing smooth changes in the target glucose
160 value so that insulin-on-board constraints are not violated. Thus, this outer loop acts as a safety
161 supervisory loop. The IOB estimation is calculated using a previous population pharmacokinetic
162 model. Finally, the IOB limit is estimated individually based on one-week CGM monitoring

163 data and previous insulin pump settings. Compared to Insulin Feedback (IF), also used in
164 combination to PID controllers [XX], SMRC is expected to induce an early pump shut-off due
165 to the augmented bolus administration with a potential benefit in PP control, as compared to a
166 later effect by IF driven by the estimated plasma insulin concentration.

167

168 *Mixed meal tests*

169 Before the meal test, fasting subjects were admitted to the clinical research units at 08:00 AM.
170 In a sitting position, two venous lines were prepared, one for arterialized venous blood sampling
171 (18) and the other for insulin/glucose infusion, if required. To ensure comparable metabolic
172 conditions between studies, where appropriate, subjects received an intravenous infusion of
173 regular human insulin in a feedback fashion, or glucose, to maintain plasma glucose at 90-100
174 mg/dl until the beginning of the studies. At 12:00 h (t=0), a standard mixed meal (530 Kcal, 60g
175 CHO, 45.3% CHO, 24.2% protein, 30.5% fat) was consumed in 15-20 minutes. At the same
176 time, insulin was administered following the randomization protocol (OL or CL), and plasma
177 glucose was monitored for the ensuing eight hours until the end of study at 20:00 h (time 480
178 min). If plasma glucose fell below 70 mg/dl during two consecutive 15-min periods, oral
179 glucose was administered in fixed amounts of 15g until recovery form hypoglycemia.

180

181 *Statistical analysis*

182 Mean glucose concentrations, time spent in different ranges (< 70, 70-180 and > 180 mg/dl),
183 maximum (C_{max}) and time to maximum (T_{max}) of glucose values were used as a measure of
184 glycemic control. Variability of the postprandial glycemic response was estimated from the
185 coefficient of variation (CV) of the area under the curve (AUC) of PG and CGM values and
186 from the analysis of the glucose-time series of the four studies (CL1, CL2, OL1, OL2).

187 The primary study variable was the CV of PG during the whole PP period ($CV\_AUC\text{-}PG_{0\text{-}8h}$).
188 However, the CV of glucose measurements was also calculated for the early ($CV\_AUC\text{-}PG_{0\text{-}3h}$)
189 and the late ($CV\_AUC\text{-}PG_{3\text{-}8h}$) postprandial phases.

All of the above measures were also calculated from CGM values.

The linear trapezoidal rule was used to calculate the AUC for glucose measurements for each study, obtaining two values for the CL (AUC_CL1 AUC_CL2) and two for the OL condition (AUC_OL1, AUC_OL2). Then CV was calculated as the ratio between the respective AUC's SDs and means, so that CV_CL= $\frac{SD\ (AUC_{CL})}{\mu\ (AUC_{CL})}$ and CV_OL= $\frac{SD\ (AUC_{OL})}{\mu\ (AUC_{OL})}$.

C_{max}, T_{max} and the time spent in range (70-180 mg/dl) were read directly from the concentration-time data for each subject.

As data were mostly not normally distributed, they were analyzed non-parametrically. The Wilcoxon signed rank-sum test was used to compare CVs of CL and OL studies. Glucose concentration time series, as well as all the other parameters, were analyzed using Kruskal-Wallis One-Way ANOVA on Ranks. Post-hoc comparisons were carried out to examine the differences between pairs of groups after Kruskal-Wallis analysis: the Least Significant Difference (LSD) post hoc test was used to explore all possible pair-wise comparisons of means (OL1 vs. OL2, OL1 vs. CL1, OL1 vs. CL2, OL2 vs. CL1, OL2 vs. CL2, CL1 vs. CL2).

Data analysis was carried out with SPSS software, version 20.0 (SPSS Inc., Chicago IL, USA).

Sample size calculation.

A power analysis was conducted. A one-sided t-test achieves 90% power to infer that the mean difference is not 0.000 when the total sample size of a cross-over design is 20, the actual mean difference is -4.813, the square root of the within mean square error is 5.000, and the significance level is 0.05.

Results

Twenty subjects with T1DM with fair glycemic control (13/7, females/males; age 40.7±10.4 (mean±SD) years; BMI 25.7±3.0 kg/m^2; diabetes duration 22.2±9.9 years; time on CSII 7.2±4.4 years; HbA1c 7.8±0.7%) were recruited and all of them completed the study.

Efficacy - glycemic control

Analysis of CV_AUCs did not show any improvement of glucose variability using CL as compared to OL, with values around 10% either with PG or CGM independently of the PP period phase (0-8h, 0-3h, 3-8h) (Table 1). However, analysis of glucose concentration time series was superior with a controller-driven insulin infusion. Indeed, PG was significantly lower in CL than in OL (OL1 152.4±53.4; OL2 159.3±53.8; CL1 123.3±46.9; CL2 124.9±44.3 mg/dl, $p<0.0001$), with no differences between CL studies (CL1-CL2 =-1.6 mg/dl with 95%CI [-6.9; 3.8]). In contrast, mean PG during OL1 was significantly different from OL2 (-6.9 mg/dl [(-12.3; -1.5]). The differences between OL and CL studies were also confirmed when CGM time series were analyzed (OL1 160.8±51.8; OL2 165.2±56.7; CL1 132.1±47.8; CL2 127.1±42.3mg/dl, $p<0.0001$). However, in this case post-hoc analysis revealed no difference between OL (OL1-OL2 -4.4 mg/dl [-9.7; 1]) or between CL studies (CL1-CL2 -5 mg/dl [-0.4; 10.4]).

Time spent in range (70-180 mg/dl) calculated either in PG or CGM values, was significantly greater (80 vs. 64% PG; 78.8 vs. 60.5% CGM, $p<0.05$) in CL as compared to OL, without any significant difference in the time spent in hypoglycemia (6.1 vs. 3.2% PG; 5.2 vs. 1.9% CGM, $p<0.05$) (Table 2). Additionally, Cmax was significantly lower in CL studies either considering PG (OL 217.1±67.0 vs. CL 183.3±63.9, $p=0.00029$) or CGM data (OL 227.4±66.7 vs. CL 196.2±59.4, $p<0.0001$), without any difference between CL (CL1=CL2) or OL (OL1=OL2) studies (p=NS for post-hoc analysis).

Safety – hypoglycemic episodes

The mean amount of oral glucose given to recover from mild hypoglycemic episodes did not differ between studies (OL 7.2±83.3g vs. CL 12.8±114.2g, $p=0.121$). Although numerically greater, the percentage of studies in which oral glucose was needed (40% vs 22.5%), as well as the mean number of rescues (0.825±1.20 vs 0.5±1.18, $p=0.054$) was not significantly different

in CL as compared to OL studies. A shift from primary to secondary CGM was infrequent and also there was no need to feed the CL using reference data.

Insulin dose

The mean total insulin dose (OL 0.198±0.933 vs. CL 0.209±0.987, U/kg; $p<0.0001$) and the mean basal insulin dose (OL 0.089±0.049 vs. CL 0.097±0.106, CL2 0.093±0.098 U/kg; $p<0.0001$) were significantly greater in CL as compared to OL studies (Figure 2). However, the mean global difference in daily doses was numerically small with a size effect of 2.2%. The overall ratio of basal to prandial insulin during the experiments was 44.6/55.4 % in OL vs. 45.3/54.7% in CL studies.

Conclusions

Our study shows that the novel SMRC-based CL algorithm improved glucose control consistently and safely across the early and late postprandial phase without increasing hypoglycemia risk. Glucose variability was relatively small in both study arms and was not improved in CL as compared to standard treatment.

Improvement of PP hyperglycemia avoiding late hypoglycemia is one of the main challenges of all the groups involved in AP research. Intra-patient variability, errors in glucose sensor measurements, and, mainly, the delay in the control action are some of the limiting barriers. However, to our knowledge, studies comparing OL vs. CL more than once and only during the PP period in controlled conditions are very scarce.

Many hybrid blood glucose control systems include a feed-forward action as a full standard bolus or a portion of the bolus for safety reasons. To reduce postprandial peaks induced by large meals or foods with a large glycemic index, Walsh et al. (19) proposed the delivery of a "superbolus", increasing the standard bolus and then reducing the basal insulin rate over a period of time. However, direct demonstration of the effectiveness of this approach has not been provided in the OL or in the CL setting.

An OL approximation to the superbolus is the so-called iBolus, a methodology for CGM-based calculation of the prandial insulin dose, which results on most occasions in a greater-than-usual bolus followed by a transient reduction of basal infusion. The iBolus was validated in a previous study (20) showing that the use of an OL "superbolus" is feasible and efficient when combined with a proper subsequent decrease of the basal insulin controlling small meals (40 g CHO).

Chase et al. (21) showed that adding 30% to insulin bolus calculated by I:CH ratio was the best option to control PP glycemic excursion in comparison to either a standard bolus or a bolus 15 minutes before the meal in CL studies. Nevertheless, postprandial hyperglycemic excursions in that study were much higher than in our study (glucose peak 220 vs 183 mg/dl, respectively). A different approach, focused on the reduction of the incidence of postprandial hypoglycemia, was adopted by Elleri et al. (22). They compared CL therapy with a 25% reduction of prandial boluses against standard prandial insulin boluses. However, hypoglycemia was very rare in both groups and no demonstration of greater safety was found.

Regarding our SMRC-based algorithm, it was previously evaluated in a cohort of ten adult virtual patients in a 16-h protocol (8:00 to 24:00 h), including three meals in 10 days. With this algorithm, potentially severe hypoglycemic events (< 50 mg/dl) were almost inexistent, the percentage of time < 70 mg/dl was reduced more than a half and there was not an increase in time > 180 mg/dl (13). Certainly, our study was intended to translate these in silico results into a clinical study protocol. The protocol was designed to evaluate the performance of a new CL algorithm in improving postprandial glycemic control (time spent in desired ranges) and intra-subject glucose variability. In our study, an augmented prandial bolus was given in the context of a SMRC CL system that limits insulin delivery when IOB is unacceptably high independently of glycemic value. As a consequence, delivery of a "superbolus" was immediately translated into a basal infusion shut-off, due to the glucose target modulation triggered by the violation of the IOB limit by the bolus. Basal infusion was then restored driven by the PID controller once IOB returned to values below limit. The main advantage of our CL system was that it significantly reduced both early and late postprandial hyperglycemia

297 exposure (>50% reduction in time spent >180 mg/dl) without a significant increased risk of
298 hypoglycemia.

299 The critical point in the SMRC controller is the adjustment of the IOB limit. Too high values
300 may cause the outer loop being inactive and ineffective reducing the risk of hypoglycemia. On
301 the other side, too small values can make the internal control loop irrelevant. A general tuning
302 of the IOB limit will lead to different values according to different situations: postprandial state,
303 exercise, night control, etc. We would like to emphasize that due to its nature the algorithm for
304 CL control based SMRC may be combined to main CL controllers of any nature, offering thus a
305 generalized safety system to avoid overcorrection problems, including PP glucose control. An
306 additional advantage of this approach is that the SMRC loop does not affect the structure of the
307 inner controller, which could be designed independently. Finally, the SMRC loop may allow
308 also a more aggressive tuning of the inner controller if necessary.

309 Glycemic variability was another objective of our study. From our results, our CL algorithm did
310 not improve glucose variability. However, the analysis of temporal series showed that
311 differences on PG values between the repeated CL studies were lower than those observed in
312 the OL experiments, suggesting a higher reproducibility of CL results. Importantly, the efficacy
313 of CL controllers against glucose variability has not been specifically evaluated in previous
314 studies. For instance, the 48-hour duration out-patient study published by Van Bon et al.
315 included repeated meals, but they were not controlled regarding the composition and pre-
316 prandial conditions, making comparisons with our study difficult (2). Some recently long-term
317 free-living studies have evaluated daytime glycemic variability. Although the PP periods were
318 not systematically investigated in Thabit et al (5), this study showed a reduction of inter-day
319 daytime variability expressed as CV from 19% with OL to 16% with CL in the adult cohort. It
320 should be noticed that variability in that study was nearly twice greater as compared with our
321 study, probably due to the highly controlled conditions of our study, which make any
322 improvement of PP variability very difficult.

The use of our CL controller was associated with a clinically marginal increase in the total insulin dose (average 0.015 U/kg body weight). This finding is not enough to explain the beneficial effect observed on PP glucose excursions with CL, indicating indirectly that not only the total insulin dose but also how insulin infusion was implemented contribute to glucose control.

We are aware that our study has some limitations. It was designed and performed in a clinical research in-patient environment including a manually implemented controller action in a currently context of fully automatic control at-home studies. However, our new CL controller needed to fulfill regulatory conditions before moving to an outpatient scenario. We used a single meal with a specific composition, which was given in a specific timeframe of the day. This limits extrapolation of results to other meal composition and daily life conditions.

In summary, our CL algorithm is able to effectively, consistently and safely control the PP glycemic excursions diminishing hyperglycemia in the post absorptive state without a clinically meaningful increasing risk of hypoglycemia. Future studies including those in transitional settings and also at-home are necessary to further validate our results in free daily life conditions.

Author Contributions: C.Q., P.R. designed the project, performed the experiments, researched data, wrote manuscript, contributed to discussion and reviewed/edited manuscript. V.M., A.C., F.L., E.M. researched data, reviewed manuscript. M.G., F.J.AB., I.C., J.B. and J.V., designed the project, researched data, wrote manuscript, contributed to discussion and reviewed/edited manuscript.

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References

1. **Van Bon AC, Jonker LD, Koebrugge R, et al.** Feasibility of a bihormonal closed-loop system to control postexercise and postprandial glucose excursions. *J Diabetes Sci Technol* 2012;6(5):1114–1122.

2. **Van Bon AC, Luijf YM, Koebrugge R, et al.** Feasibility of a portable bihormonal closed-loop system to control glucose excursions at home under free-living conditions for 48 hours. *Diabetes Technol Ther* 2014;16(3):131–136.

3. **Mauseth R, Hirsch IB, Bollyky J, et al.** Use of a "fuzzy logic" controller in a closed-loop artificial pancreas. *Diabetes Technol Ther* 2013;15(8):628–633.

4. **Del Favero S, Bruttomesso D, Di Palma F, et al.** First use of model predictive control in outpatient wearable artificial pancreas. *Diabetes Care* 2014;37(5):1212–1215.

5. **Thabit H, Tauschmann M, Allen JM et al.** Home Use of an Artificial Beta Cell in Type 1 Diabetes. *N. Engl. J. Med.* 2015;373(22):2129-40.

6. **El-Khatib FH, Russell SJ, Magyar KL, et al.** Autonomous and continuous adaptation of a bihormonal bionic pancreas in adults and adolescents with type 1 diabetes. *J. Clin. Endocrinol. Metab.* 2014;99(5):1701–1711.

7. **Sherr JL, Patel NS, Michaud CI, et al.** Mitigating Meal-Related Glycemic Excursions in an Insulin-Sparing Manner During Closed-Loop Insulin Delivery: The Beneficial Effects of Adjunctive Pramlintide and Liraglutide. *Diabetes Care* 2016;39(7):1127–1134.

8. **Zisser H, Dassau E, Lee JJ, et al.** Clinical results of an automated artificial pancreas using technosphere inhaled insulin to mimic first-phase insulin secretion. *J Diabetes Sci Technol* 2015;9(3):564–572.

9. **Del Favero S, Place J, Kropff J, et al.** Multicenter outpatient dinner/overnight reduction of hypoglycemia and increased time of glucose in target with a wearable artificial pancreas using modular model predictive control in adults with type 1 diabetes. *Diabetes, Obesity and Metabolism* 2015;17(5):468–476.

10. **Steil GM, Palerm CC, Kurtz N, et al.** The effect of insulin feedback on closed loop glucose control. *J. Clin. Endocrinol. Metab.* 2011;96(5):1402–1408.

11. **Haidar A, Legault L, Dallaire M, et al.** Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. *CMAJ* 2013;185(4):297–305.

12. **Blauw H, van Bon AC, Koops R, et al.** Performance and safety of an integrated bihormonal artificial pancreas for fully automated glucose control at home. *Diabetes,*

Obesity and Metabolism 2016;18(7):671–677.

13. **Revert A, Garelli F, Pico J, et al.** Safety auxiliary feedback element for the artificial pancreas in type 1 diabetes. *IEEE Trans. Biomed. Eng.* 2013;60(8):2113–2122.

14. **Kropff J, Del Favero S, Place J, et al.** 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. *Lancet Diabetes Endocrinol* 2015:1–9.

15. **Jansa M, Quirós C, Giménez M, et al.** Psychometric analysis of the Spanish and Catalan versions of a questionnaire for hypoglycemia awareness. *Medicina Clinica* 2015;144(10):440–444.

16. **Walsh J, Roberts R, Bailey T.** Guidelines for insulin dosing in continuous subcutaneous insulin infusion using new formulas from a retrospective study of individuals with optimal glucose levels. *J Diabetes Sci Technol* 2010;4(5):1174–1181.

17. **Walsh J, Roberts R, Bailey T.** Guidelines for optimal bolus calculator settings in adults. *J Diabetes Sci Technol* 2011;5(1):129–135.

18. **McGuire EA, Helderman JH, Tobin JD, et al.** Effects of arterial versus venous sampling on analysis of glucose kinetics in man. *J Appl Physiol* 1976;41(4):565–573.

19. **Walsh J, Roberts R.** *Walsh: Pumping insulin.* 5th Edition. Torrey Pines Press. San Diego CA. 2012

20. **Rossetti P, Ampudia-Blasco FJ, Laguna A, et al.** Evaluation of a novel continuous glucose monitoring-based method for mealtime insulin dosing--the iBolus--in subjects with type 1 diabetes using continuous subcutaneous insulin infusion therapy: a randomized controlled trial. *Diabetes Technol Ther* 2012;14(11):1043–1052.

21. **Chase HP, Doyle FJ, Zisser H, et al.** Multicenter closed-loop/hybrid meal bolus insulin delivery with type 1 diabetes. *Diabetes Technol Ther* 2014;16(10):623–632.

22. **Elleri D, Biagioni M, Allen JM, et al.** Safety, efficacy and glucose turnover of reduced prandial boluses during closed-loop therapy in adolescents with type 1 diabetes: a randomized clinical trial. *Diabetes, Obesity and Metabolism* 2015;17(12):1173–1179.