Original article

Efficacy of dual-hormone artificial pancreas to alleviate the carbohydrate-counting burden of type 1 diabetes: A randomized crossover trial

V. Gingras\textsuperscript{a,b}, R. Rabasa-Lhoret\textsuperscript{a,b,c,d,f,*}, V. Messier\textsuperscript{a}, M. Ladouceur\textsuperscript{d}, L. Legault\textsuperscript{e}, A. Haidar\textsuperscript{a,f}

\textsuperscript{a} Institut de recherches cliniques de Montréal, Montreal, Quebec, Canada
\textsuperscript{b} Department of nutrition, Université de Montréal, Montreal, Quebec, Canada
\textsuperscript{c} Montreal Diabetes Research Center (MDRC), Montreal, Quebec, Canada
\textsuperscript{d} Research Center of the Université de Montréal Hospital Center (CRCHUM), Montreal, Quebec, Canada
\textsuperscript{e} Montreal Children’s Hospital, McGill University Health Center, Montreal, Quebec, Canada
\textsuperscript{f} Division of Experimental Medicine, McGill University, Montreal, Quebec, Canada

Received 20 April 2015; accepted 3 May 2015
Available online 10 June 2015

Abstract

\textit{Aim.} – Carbohydrate-counting is a complex task for many patients with type 1 diabetes. This study examined whether an artificial pancreas, delivering insulin and glucagon based on glucose sensor readings, could alleviate the burden of carbohydrate-counting without degrading glucose control.

\textit{Methods.} – Twelve adults were recruited into a randomized, three-way, crossover trial (ClinicalTrials.gov identifier No. NCT01930097). Participants were admitted on three occasions from 7AM to 9PM and consumed a low-carbohydrate breakfast (women: 30 g; men: 50 g), a medium-carbohydrate dinner (women: 50 g; men: 70 g) and a high-carbohydrate lunch (women: 90 g; men: 120 g). At each visit, glucose levels were randomly regulated by: (1) conventional pump therapy; (2) an artificial pancreas (AP) accompanied by prandial boluses, matching the meal’s carbohydrate content based on insulin-to-carbohydrate ratios (AP with carbohydrate-counting); or (3) an AP accompanied by prandial boluses based on qualitative categorization (regular or large) of meal size (AP without carbohydrate-counting).

\textit{Results.} – The AP without carbohydrate-counting achieved similar incremental AUC values compared with carbohydrate-counting after the low-carbohydrate content (P = 0.54) and medium-carbohydrate meals, but yielded higher post-prandial excursion levels after the high-carbohydrate meal (P = 0.004). The AP with and without carbohydrate-counting yielded similar mean glucose levels (8.2 ± 2.1 mmol/L vs. 8.4 ± 1.7 mmol/L; P = 0.52), and both strategies resulted in lower mean glucose compared with conventional pump therapy (9.6 ± 2.0 mmol/L; P = 0.02 and P = 0.03, respectively).

\textit{Conclusion.} – The AP with qualitative categorization of meal size could alleviate the burden of carbohydrate-counting without compromising glucose control, although more categories of meal sizes are probably needed to effectively control higher-carbohydrate meals.

© 2015 Elsevier Masson SAS. All rights reserved.

Keywords: Artificial pancreas; Carbohydrate-counting; Closed-loop hormonal delivery systems; Continuous glucose monitoring; Type 1 diabetes

1. Introduction

Type 1 diabetes (T1D) is a chronic disease caused by the autoimmune destruction of beta cells; it is treated by intensive insulin therapy using either multiple daily injections or an infusion pump. To reduce the risk of long-term microvascular and macrovascular complications, insulin therapy aims for tight glucose control, as assessed by glycated haemoglobin (HbA\textsubscript{1c})
values < 7%, while minimizing hypoglycaemia [1,2]. However, most patients do not achieve glycaemic targets, as shown by an average HbA1c > 8% and a high frequency of hypoglycaemia [3,4].

Current insulin therapy involves prandial boluses to cover the insulin needs of meals, and basal delivery to cover between meal and overnight insulin needs. A meal’s carbohydrate content is the main determinant of prandial insulin needs and, consequently, accurate carbohydrate-counting is recommended [5,6] and associated with better glycaemic control [7] in T1D patients. However, accurate carbohydrate-counting is a challenging task for many patients, as it has an estimation error of around 20% [8].

Artificial pancreas systems are emerging technologies to treat T1D [9], and two configurations have been proposed: one infuses insulin [10]; and the other infuses insulin and glucagon [11]. Artificial pancreas systems direct insulin and glucagon delivery based on glucose sensor readings, and improve glucose control compared with conventional therapies [9–14]. Early artificial pancreas studies attempted to avoid carbohydrate-counting by omitting prandial boluses and relying exclusively on glucose sensor readings to cover meal-related insulin needs [15,16]. However, due to delays in rapid-acting insulin absorption [17,18] compared with meal glucose absorption, this approach resulted in prolonged hyperglycaemia [15,16], although more advanced dosing algorithms are currently being investigated [19]. An alternative approach that would also avoid carbohydrate-counting, but which necessitates announcing the meal to the algorithm, is to give a partial prandial bolus regardless of the carbohydrate content of the meal and, instead, dependent on, for example, body weight, total daily insulin or insulin-to-carbohydrate ratio. The artificial pancreas would then adjust its basal insulin delivery on the basis of glucose readings to provide postprandial insulin. This approach achieves better postprandial control than complete omission of the prandial bolus [15,20,21].

Although the artificial pancreas accompanied by partial boluses eliminates the need for precise carbohydrate-counting, this benefit should be obtained without degrading glucose control. Our team has previously shown that a weight-dependent partial bolus can be associated with larger postprandial carbohydrate excursions compared with a carbohydrate-matching bolus after a large breakfast [22]. No other study has compared partial bolus strategies with carbohydrate-matching boluses. For this reason, the present study compared:

- an artificial pancreas accompanied by a partial bolus strategy based on qualitative meal size assessment while taking into account individualized insulin-to-carbohydrate ratios (artificial pancreas without carbohydrate-counting);
- an artificial pancreas accompanied by carbohydrate-matching boluses (artificial pancreas with carbohydrate-counting);
- conventional pump therapy accompanied by carbohydrate-matching boluses.

Our hypothesis was that the artificial pancreas without carbohydrate-counting would achieve comparable control to the artificial pancreas with carbohydrate-counting, and both these strategies would be superior to conventional pump therapy.

2. Methods

2.1. Study design

This was an open-label randomized, three-way, crossover study to compare the efficacy of an artificial pancreas requiring no carbohydrate-counting, an artificial pancreas accompanied by carbohydrate-counting, and conventional pump therapy with carbohydrate-counting in regulating glucose levels in adults with T1D (ClinicalTrials.gov identifier No. NCT01930097).

2.2. Study population

Patients were recruited from October 2013 to February 2014, and tested at the Institut de Recherches Cliniques de Montréal (IRCM; Clinical Research Institute of Montreal) in Quebec, Canada. Included were adults (≥18 years of age) with T1D for at least a year and using insulin pump therapy for at least 3 months. Poorly controlled patients (HbA1c ≥ 12%) and patients with gastroparesis were excluded. Other exclusion criteria were applied as detailed in the clinical trial registry. The IRCM ethics committee approved the study, and all participants provided their informed written consent.

2.3. Study procedures

Study participants underwent a complete medical examination at the screening visit. Their basal rates and insulin-to-carbohydrate ratios were optimized by a registered nutritionist over the following 10 days, if needed.

The three interventional visits were separated by 3–30 days. For each visit, patients fasted from midnight of the previous night and were then admitted to a clinical research facility from 0700 to 2100 h. Standardized meals were served at 0800 h (50 g of carbohydrate for men; 30 g of carbohydrate for women), 1200 h (120 g of carbohydrate for men; 90 g of carbohydrate for women) and 1700 h (70 g of carbohydrate for men; 50 g of carbohydrate for women). Patients had two options for each meal and consumed the selected meal on all three interventional visits (Appendix A has a description of the meals and their full macronutrient composition, see supplementary material associated with this article online). Between meals, patients were allowed to do sedentary activities (such as reading, watching television, playing video games). Between 1600 and 1700 h, patients were allowed to take a leisurely walk.

On admission, the patients’ pumps were substituted with the study pump (ACCU-CHEK® Combo system, Roche Diagnostics, Basel, Switzerland), and a cannula was inserted into an arm vein for blood sampling. Venous blood samples were taken every 20 min from 0700 to 2100 h for determination of plasma glucose, in duplicate, using the YSI 2300 STAT Plus Analyzer (YSI Life Sciences, Yellow Springs, OH, USA). If plasma glucose fell to < 3.6 mmol/L, the sampling rate was increased to every 10 min until levels were again > 3.6 mmol/L; 15 g of oral
carbohydrate were given if plasma glucose dropped to <3.3 mmol/L with hypoglycaemia symptoms or to <3.0 mmol/L regardless of symptoms or not. Participants were blinded to hormonal infusions during artificial pancreas visits, and to interstitial and plasma glucose readings during all interventions.

During conventional pump therapy visits, subjects adjusted insulin aspart delivery (NovoRapid®, Novo Nordisk, Mississauga, Canada) as per their standard practice, including temporary basal and correction boluses. They had access to their finger-stick glucose measurements and were advised to measure their glucose levels as per usual. The carbohydrate contents of meals were revealed to participants to allow them to deliver their boluses based on their insulin-to-carbohydrate ratios, as calculated by the pump bolus wizard.

During both artificial pancreas visits, glucose levels were regulated using a dual-hormone (insulin and glucagon) closed-loop delivery system. Insulin aspart and recombinant glucagon (Glucagen®, Paladin Labs Inc., Montreal, QC, Canada) were delivered using two subcutaneous infusion pumps. Glucose levels were measured by a glucose sensor (Enlite Sensor®, Medtronic MiniMed, Inc., Northridge, CA, USA), which was calibrated against capillary glucose measurements. Real-time sensor readings were entered manually into a laptop computer every 10 min, which generated recommendations for basal insulin and glucagon mini-boluses. The recommended basal and bolus delivery rates were then manually delivered via the pumps. The recommendations were generated based on a predictive algorithm, which has been described and tested in previous studies [11,23]. The algorithm was initialized using body weight, daily insulin requirements and insulin-to-carbohydrate ratios.

On visits where the artificial pancreas was accompanied by carbohydrate-counting, prandial boluses were calculated using individualized insulin-to-carbohydrate ratios multiplied by the meal carbohydrate content. Moreover, the meal carbohydrate contents and prandial boluses were entered into the algorithm, which included them in its calculations of postprandial basal insulin and glucagon boluses.

On visits where the artificial pancreas was not accompanied by carbohydrate-counting, prandial boluses were calculated using individualized insulin-to-carbohydrate ratios and qualitative meal size assessment. Meals were assessed as either (1) ‘regular’ or (2) ‘large’. Regular meals were defined as any meal with <60 g of carbohydrates, while large meals were those with >60 g of carbohydrates. For all regular meals, prandial boluses were calculated as individualized insulin-to-carbohydrate ratios multiplied by 35. For all large meals, prandial boluses were calculated as insulin-to-carbohydrate ratios multiplied by 65. Meal size assessments (regular or large) and prandial boluses were entered into the algorithm, which used these data to calculate the postprandial basal insulin and glucagon boluses.

2.4. Outcomes

The primary study outcome was the 4-h post-meal incremental area under the curve (iAUC) for each ingested meal during the two artificial pancreas interventions (with and without carbohydrate-counting). Secondary outcomes were percentage of time that plasma glucose was within the target range (4.00–10.00 mmol/L), mean blood glucose concentration, percentage of time spent below the target range, percentage of time spent above the target range, total amount of insulin delivered, the standard deviation (SD) of plasma glucose concentrations and the number of participants with hypoglycaemic events requiring treatment (plasma glucose <3.0 mmol/L regardless of symptoms or not, or <3.3 mmol/L with symptoms). All comparisons between the artificial pancreas interventions and conventional pump therapy were secondary and for exploratory purposes only and, therefore, did not require multiplicity adjustment.

2.5. Calculation of sample size and randomization

Our present study was powered to detect a mean interventional difference of 0.75 mmol/L for our primary endpoint (iAUC at 4-h post-meal). It was estimated, based on data from our previous study [22], that the SD of the paired differences in AUC would be 0.8 mmol/L. After correcting for multiple comparisons using the Bonferroni method, power calculations revealed that 12 subjects were necessary to achieve an 80% statistical power. Block randomization, created by a third party unrelated to the project, was used with an equal allocation ratio to generate allocation sequences. Patients were blinded to bolus type during the artificial pancreas visits, but not to the type of intervention (artificial pancreas vs. conventional pump therapy).

2.6. Statistical analyses

Pairwise comparisons for our primary endpoints were estimated from a linear mixed-effect model with treatment, period, sequence and starting glucose levels as fixed effects, and individuals as random effects. All pairwise comparisons for our secondary continuous outcomes were similarly estimated. Endpoints that did not respect normality assumptions were log-transformed. Bonferroni adjustments were made for multiple comparisons of the primary outcome, where statistical significance was defined as $P < 0.0167$ (0.05/3). Data are presented as medians (interquartile range [IQR]) or means ± SD.

3. Results

Twelve participants completed the study and were included in the analysis (Fig. 1). Participants (50% men and 50% women) were 51.3 ± 14.8 years old, with HbA1c values of 7.4 ± 0.9% and duration of diabetes of 32.6 ± 13.9 years (Table 1).

Fig. 2 shows plasma glucose profiles as well as insulin and glucagon deliveries. Plasma glucose was initially lower during visits involving the artificial pancreas without carbohydrate-counting compared with visits of conventional pump therapy and the artificial pancreas with carbohydrate-counting (6.2 vs. 8.4 and 8.0, respectively; $P = 0.04$ and $P = 0.048$, respectively, for both comparisons; Table 2). Analyses of mean plasma glucose and time spent within specific glucose ranges thus adjusted
for starting plasma glucose. The primary outcome, the iAUC, is also corrected for starting glucose level.

For post-meal glucose control, both artificial pancreas strategies yielded similar glucose excursions (as measured by iAUC) after breakfast and dinner (small and medium meals, respectively). After lunch (a large meal), the artificial pancreas without carbohydrate-counting yielded higher post-meal excursions than the artificial pancreas with carbohydrate-counting (glucose AUC: 3.32 vs. 1.44 mmol/L; \( P=0.004 \); Table 2). No significant difference was observed between conventional therapy and both artificial pancreas strategies in glucose excursions for all three meals \( (P>0.05; \text{Table } 2) \).

Also, no difference between the two artificial pancreas interventions (with and without carbohydrate-counting) was observed for mean plasma glucose and time spent within the target range of 4.0–10.0 mmol/L \( (P>0.05; \text{Table } 2) \). Moreover, the artificial pancreas without carbohydrate-counting achieved a lower mean plasma glucose and greater time spent in the target range compared with conventional pump therapy [mean glucose: 8.4 vs. 9.6 mmol/L \( (P=0.02) \); time within target: 64.2% vs. 49.9% \( (P=0.03) \); Table 2]. No significant difference was observed related to the order of the intervention (data not shown).

As expected with the interventions, bolus insulin delivery was lower with the artificial pancreas with no carbohydrate-counting compared with conventional pump therapy as well as the artificial pancreas with carbohydrate-counting \( (P<0.001; \text{Table } 2, \text{Fig. } 2) \). However, slightly more insulin boluses were given during conventional therapy than during the artificial pancreas with carbohydrate-counting (22.5 U vs. 20.6 U; \( P=0.02; \text{Table } 2) \), despite identical meal intakes and insulin-to-carbohydrate ratios. This difference was due to additional correction boluses taken at meal times or between meals by patients using conventional pump therapy. Seven (58%) of the participants took at least one correction bolus between meals during conventional therapy visits (total: 11 boluses). As expected, larger basal insulin delivery was observed with the artificial pancreas without carbohydrate-counting (14.4 U) than with either conventional therapy (9.8 U; \( P=0.004 \)) or the artificial pancreas with carbohydrate-counting (10.5 U; \( P<0.001; \text{Table } 2, \text{Fig. } 2) \). Total insulin delivery was lower with the artificial pancreas without carbohydrate-counting than with conventional pump therapy and the artificial pancreas with carbohydrate-counting (Table 2).

Fig. 3 shows the percentage of participants with plasma glucose > 10.0 mmol/L during the course of our experiment. The percentage of time that plasma glucose was > 10.0 mmol/L was similar during both artificial pancreas visits (21% vs. 29% without carbohydrate-counting: \( P=0.36; \text{Table } 2 \) and lower than during conventional treatment visits (41%; \( P=0.03 \) vs. with carbohydrate-counting: \( P=0.09 \) vs. without carbohydrate-counting; Table 2).

The percentage of time spent at < 4.0 mmol/L did not differ significantly across the three interventions \( (P>0.05; \text{Table } 2) \). However, two participants (16%) had hypoglycaemia requiring oral treatment (< 3.3 mmol/L with symptoms or < 3.0 mmol/L regardless of symptoms) with the artificial pancreas and no carbohydrate-counting (four events) compared with four participants (33%) with the artificial pancreas and carbohydrate-counting (eight events), and four participants (33%) using conventional therapy (six events). One participant accounted for nearly half the events, experiencing three events with the artificial pancreas without carbohydrate-counting, four events with the artificial pancreas with carbohydrate-counting and two events with conventional therapy. At times of hypoglycaemia events during artificial pancreas visits (total: 12 events), the sensor overread by a median of 2.2 mmol/L during visits without carbohydrate-counting (sensor value was > 4.7 mmol/L for
Fig. 2. Patient profiles (medians and interquartile ranges) of (upper) plasma glucose and (middle) insulin delivery, and (lower) histogram of glucagon delivery. AP: artificial pancreas; CHO: carbohydrate; 50M–30W g/120M–90W g/70M–50W g: men 50 g, women 30 g; men 120 g, women 90 g; men 70 g, women 50 g.

all events) and by 1.6 mmol/L during visits with carbohydrate-counting (sensor value was >4.0 mmol/L for all events except one at 3.7 mmol/L). This indicates that hypoglycaemic events with the artificial pancreas were related to sensor overreadings rather than recommendations made by the dosing algorithm. Fig. 2 shows these hypoglycaemic events in a series of graphs.

The amounts of glucagon delivered were similar during both artificial pancreas visits—with carbohydrate-counting, 0.044 mg (0.0–0.076 mg) vs. without carbohydrate-counting, 0.042 mg (0.033–0.089 mg); P = 0.75— but their distribution was different. Although most of the glucagon was given during the late postprandial period during both artificial pancreas visits, glucagon was more often delivered in the early postprandial period when carbohydrate-counting was used. Without carbohydrate-counting, only 7% of the glucagon was delivered within the first 2 h postprandially (29% for 3 h postprandially) compared with 14% when carbohydrate-counting was involved (51% for 3 h postprandially). The size of the glucagon boluses did not differ between the two artificial pancreas visits: with carbohydrate-counting, 0.013 mg (0.010–0.019 mg) vs. without carbohydrate-counting, 0.013 mg (0.011–0.019 mg). Also, no participant reported any symptoms following glucagon boluses.
Table 2
Comparison of all study interventional outcomes for 12 adults with type 1 diabetes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention, median (IQR)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-meal glucose iAUC, mmol/L&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Breakfast: 1.11 (0.33–2.29)</td>
<td>1.31 (0.20–3.32)</td>
</tr>
<tr>
<td></td>
<td>Lunch: 1.44 (–0.34–1.88)</td>
<td>3.32 (0.88–4.46)</td>
</tr>
<tr>
<td></td>
<td>Dinner: 1.01 (0.45–1.76)</td>
<td>0.44 (–1.2–1.73)</td>
</tr>
<tr>
<td></td>
<td>Plasma glucose at start of visit, mmol/L</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Plasma glucose level, mmol/L, mean ± SD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.2 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>SD of plasma glucose level, mmol/L, median (IQR)</td>
<td>2.4 (1.5–3.8)</td>
</tr>
<tr>
<td>Time spent at specific glucose level, %&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Target range&lt;sup&gt;d&lt;/sup&gt;: 66.8 (56.2–79.7)</td>
<td>64.2 (54.1–75.3)</td>
</tr>
<tr>
<td></td>
<td>&lt;4.0 mmol/L: 0.1 (0.0–8.7)</td>
<td>5.4 (0.0–8.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;10.0 mmol/L: 20.7 (11.3–39.3)</td>
<td>29.3 (16.2–40.0)</td>
</tr>
<tr>
<td>Insulin delivery</td>
<td>Basal insulin delivery, U: 10.5 (9.4–16.5)</td>
<td>14.4 (12.6–17.7)</td>
</tr>
<tr>
<td></td>
<td>Bolus insulin delivery, U: 20.6 (17.7–24.5)</td>
<td>14.4 (12.4–17.2)</td>
</tr>
<tr>
<td></td>
<td>Total insulin delivery, U: 33.0 (27.8–41.1)</td>
<td>29.5 (26.1–36.1)</td>
</tr>
<tr>
<td>Glucagon delivery, mg</td>
<td>0.044 (0.00–0.08)</td>
<td>0.042 (0.03–0.09)</td>
</tr>
</tbody>
</table>

IQR: interquartile range; AP: artificial pancreas; CSII: continuous subcutaneous insulin infusion (pump therapy); iAUC: incremental area under the curve; SD: standard deviation.

<sup>a</sup> Linear mixed-model analyses.
<sup>b</sup> Primary endpoint was comparison of two AP strategies.
<sup>c</sup> 4.0–10.0 mmol/L.
<sup>d</sup> Model further adjusted for starting plasma glucose.

Fig. 3. Graph showing percentages of patients with glucose > 10 mmol/L between 0800 h and 2100 h. AP: artificial pancreas; CHO: carbohydrate; 50 M–30 W g/120 M–90 W g/70 M–50 W g: men 50 g, women 30 g/men 120 g, women 90 g/men 70 g, women 50 g.

4. Discussion

Our study tested whether a simplified bolus strategy using an artificial pancreas could result in comparable glucose control in comparison to the standard carbohydrate-matching bolus strategy. With the simplified strategy, glucose control was comparable to the carbohydrate-matching bolus after small and medium meals (as assessed by iAUC), but led to larger excursions after the large meal. In an exploratory analysis, both artificial pancreas strategies resulted in lower mean glucose and more time spent within the target range compared with conventional pump therapy.

Most strategies aiming to eliminate carbohydrate-counting with the artificial pancreas used body weight to determine
the aggressiveness of prandial boluses [15,20,22], but our present study used insulin-to-carbohydrate ratios instead. This choice was based on a secondary analysis from our previous study [22], which showed that, when body weight is used, the prandial bolus led to bigger glucose excursions (compared with a carbohydrate-matching bolus) proportionally to individualized insulin-to-carbohydrate ratios. Moreover, using insulin-to-carbohydrate ratios benefits from the ability: (a) to have different levels of aggressiveness at different times of the day; and (b) to individualize the aggressiveness level for subjects with the same body weight. These are important factors, given the diurnal patterns and interindividual variability of postprandial insulin requirements [24]. Operation over multiple days would also allow estimation algorithms to optimize insulin-to-carbohydrate ratios automatically.

Although the same amounts of glucagon were delivered, their distribution differed between the two artificial pancreas interventions. In the early postprandial period, glucagon was delivered more often following the carbohydrate-matching boluses than after non-matched boluses. Also, glucagon delivery during both artificial pancreas interventions did not significantly reduce either time spent in hypoglycaemia or postprandial hypoglycaemic events compared with conventional pump therapy, as had been expected from our previous studies using the same algorithm for the postprandial phase [11,23]. This was mostly due to sensor overreadings, as most hypoglycaemic events, except one, happened when sensor readings were >4 mmol/L. Moreover, one participant was responsible for 70% of all events (7/10) during the artificial pancreas interventional visits. Increased sensor accuracy should reduce such postprandial hypoglycaemic episodes.

Our present study has several limitations. First, our strategy led to bigger glucose excursions after the large meal compared with carbohydrate-matching boluses. This was due to the large mismatch between the two prandial boluses (9.6 U vs. 5.7 U; P < 0.001), which might be mitigated by having more qualitative meal size categories, such as ‘regular’, ‘large’ and ‘very large’ as opposed to only ‘regular’ and ‘large’, with the ‘very large’ category associated with larger boluses. Second, our study was conducted in an inpatients setting in which the intervention with carbohydrate-counting relied on counting accuracy. As real-life counting errors are in the order of around 20% [8], our present findings need to be confirmed in outpatients studies. Third, although our strategy alleviated the need for precise carbohydrate-counting, qualitative meal size assessment was still necessary, indicating that a certain degree of carbohydrate-counting knowledge is still required to avoid meal size misclassification and that patients would also need to understand that a large meal denotes a carbohydrate-rich meal and not a large-quantity meal. Also, the starting glucose was statistically lower in the group with the artificial pancreas without carbohydrate-counting. Even though statistical correction was applied, it cannot be excluded that the post-breakfast glucose control and percentage of time spent at >10 mmol/L may have been affected by the divergent starting glucose concentration. Finally, our study used manual rather than laptop-based [25] or phone-based [26] automated control, although this is unlikely to have affected the clinical conclusions. Moreover, manual control resulted in robust data transmission and avoided the technical problems experienced by others [25–27], mimicking the performance of a future integrated system.

5. Conclusion

To the best of our knowledge, this was the first study to compare, over three consecutive meals, the efficacy of an artificial pancreas without carbohydrate-counting and an artificial pancreas based on the current recommendation for carbohydrate-matching prandial boluses. Unlike current therapies where non-matched prandial boluses degrade glucose control [28], our present study suggests that an artificial pancreas with qualitative categorization of meal size might alleviate the burden of carbohydrate-counting without compromising glucose control, although three categories of meal sizes are likely to be needed to effectively control very large meals.

Disclosure of interest

R.R.L. has received consultant/speaker honoraria and/or grants from AstraZeneca, Becton Dickinson (BD), Boehringer Ingelheim, Eli Lilly, Janssen, LifeScan, Medtronic, Merck, Novartis, NeoMed, Novo Nordisk, Roche, Sanofi-Aventis, Takeda and Valeant. A.H. and R.R.L. own IPs in the area of artificial pancreas. The other authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

We would first like to express our gratitude to all participants in this study. We thank Melika Forde and Cherylene Pinarc, who provided nursing support. We would also like to thank Annie Tardif, Diane Mignault, Nicolas Bougette and Anne Sarais for their support in conducting the sample analyses.

Funding: This work is supported by grants from the Juvenile Diabetes Research Foundation and J.-A. DeSève Foundation to R.R.L. V.G. and R.R.L. are research scholars of FRQS (Fondes Recherche du Québec en Santé; Quebec Health Research Fund). A.H. was a research scholar at the Juvenile Diabetes Research Foundation.

Appendix A. Supplementary data

Supplementary material (Appendix A, menus and macronutrient composition of the study meals) associated with this article can be found at http://www.sciedirect.com and http://dx.doi.org/10.1016/j.diabet.2015.05.001.

References


