Clinical Validity of Insulin Bolus Calculators

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Presenter Disclosure Information

Abbott Diabetes Care
Glooko
Tidepool
Topics for Discussion

QUESTION 1: How can patients and providers be confident that the insulin bolus values obtained from the calculators are accurate and appropriate for their use?

QUESTION 2: What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for diabetes management?

QUESTION 3: How can FDA foster both innovation and safety of insulin dose calculators intended for use by healthcare practitioners?

QUESTION 4: How can FDA foster both innovation and safety of insulin dose calculators intended for use by patients?
Topics for Discussion

QUESTION 1: How can patients and providers be confident that the *insulin bolus values* obtained from the calculators are accurate and appropriate for their use?

How is insulin often dosed in practice?
Diagnosed with diabetes summer 1922, aged 6
Died winter 2006, three weeks before 90th birthday: tennis in the morning, followed by lunch, failed to wake up from afternoon siesta

Personal experience informs what is best for individual patients
Patient is the ultimate decision-maker in day-to-day diabetes management
Clinician’s role is not simply to prescribe insulin doses, but to guide the patient in making informed dosing and diabetes self-management decisions

Collaborative - instead of prescriptive - model of care required in diabetes has implications for how many patients can be expected to use bolus calculators
Standard Insulin Replacement Regimen in T1D
Early 1990’s

Constraints: Eating had to be organized around the insulin profiles.
Insulin dosing: Relatively fixed.
Trade-off: Less flexibility in eating → often poorer adherence.
Milestones in the evolution of intensive insulin therapy:

- **1993**: DCCT
- **1995**: Introduction of 1st analog insulin (Lispro)
- **2003**: Introduction of 1st pump with bolus calculator (Deltec Cozmo)
The Current Approach: Food Insulin Dose Calculation

Carbohydrate quantity \times \text{Insulin-to-Carb ratio} = \text{Insulin dose}

This dosing formula - which is incorporated in current insulin bolus calculators - has never been scientifically validated.

Does this approach work in practice?
Yes….but, not as well as is supposed
Carbohydrate quantity $\times$ Insulin-to-Carb ratio = Insulin dose

Is accuracy in carb counting a realistic goal for most patients?
Carbohydrate counting skills in adult pump patients at Joslin

HbA1c

Patient estimated quantity (grams)

30 grams
Limitations and Assumptions.....

Carbohydrate quantity \times \text{Insulin-to-Carb ratio} = \text{Insulin dose}

Is accuracy in carb counting a realistic goal for most patients?

Assumes that carbs are the only dietary ingredient that affects insulin requirements. Is there any scientific validity to carb-based insulin dosing?

Assumes that getting the insulin dose correct is all that matters. To achieve optimal postprandial glucose control insulin action needs to match carb absorption.
Insulin Pharmacodynamics

- Aspart
- Lispro

Cheerios Glycemic Index = 83

Graph showing glucose levels over time with markers for 3:00 AM, 6:00 AM, 9:00 AM, 12:00 PM, 3:00 PM, 6:00 PM, and 9:00 PM.
To optimize postprandial glucose control, sometimes need to change food choices.

Highlights the limitations of focusing on “accuracy” of bolus calculator settings alone as a key therapeutic endpoint in intensive diabetes management.
Free fatty acids induce insulin resistance

Does dietary fat increase insulin requirements?

Belfort et al, *Diabetes* 2005; 54:1640
Boden et al, *Diabetes* 2001; 50:1612
Frias et al, *Diabetes* 2001; 50:1344
Closed Loop Protocol in CRC

Admit

Open Loop

Closed Loop

Day 1

Day 2

Day 3

Lunch

Dinner

High Fat

or

Low Fat

Wolpert et al, *Diabetes Care* 2013; 36:810
Closed Loop Protocol in CRC

Admit

Open Loop

Closed Loop

Day 1

12          6p         11p          8a          12            6p        11p           8a          12

Dinner

High Fat

or

Low Fat

Breakfast

Open Loop

Closed Loop

Day 2

Dinner

High Fat

or

Low Fat

Breakfast

Closed Loop

Day 3

12          6p         11p          8a          12            6p        11p           8a          12

Lunch

Closed Loop Protocol in CRC

Wolpert et al, Diabetes Care 2013; 36:810
Dietary Fat Acutely Increases Glucose Concentrations and Insulin Requirements in Patients With Type 1 Diabetes

Implications for carbohydrate-based bolus dose calculation and intensive diabetes management

Wolpert et al, *Diabetes Care* 2013; 36:810
The current approach to food insulin dose calculation – incorporated into current bolus calculators – is not scientifically valid.

In practice, to achieve optimal glycemic control patients need to adjust the insulin dose based on other factors, including activity, dietary fat, alcohol, etc.
QUESTION 1: How can patients and providers be confident that the insulin bolus values obtained from the calculators are accurate and appropriate for their use?

All bolus dose recommendations – whether generated by a bolus calculator or derived from a paper-based algorithm – are inherently inaccurate since do not incorporate adjustments for other factors affecting prandial insulin requirements.

In practice, these bolus recommendations are starting point in insulin dosing decisions. Based on experience, patients learn whether dose is appropriate for their use.
Use Cases for Insulin Bolus Calculators

All time

- Newly-diagnosed T1D
- T1D during intensification phase (not yet confident in self-adjustment)
- Physiologically changing insulin requirements e.g. childhood/adolescence, pregnancy
- Initial dose titration e.g. introduction of basal insulin in T2D
- Hospital-based protocols
- Limited numeracy
- Impaired cognition
- Low self-management confidence

Most time

- T1D with improving self-mastery of DM management

Some time

- T1D: Maintenance phase

Rarely

- Independently minded

None

- Pre-contemplative/Disengaged from self-care
QUESTION 2: What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for diabetes management?

**CORRECTION INSULIN BOLUS CALCULATION:**

\[
\text{Current glucose} - \text{Target glucose} = \text{Correction dose} - \text{Insulin on board} = \text{Recommended Insulin dose}
\]
Effect of Different Target Glucose Goals in Bolus Calculators on Correction Dose

\[
\text{Current glucose} - \text{Target glucose} = \text{Correction dose} - \text{Insulin on board} = \text{Recommended Insulin dose}
\]

- Animas & Roche bolus calculators use mid-point of programmed target range in dose calculation
- Medtronic MiniMed bolus calculator uses upper limit of programmed target range in dose calculation

Zisser et al, DT&T 2010; 12:955
Effect of Different Target Glucose Goals in Bolus Calculators on Correction Dose

Protocol: Under-bolused for meal, corrected 2 hours later using boluses recommended by pump dose calculator

Head-to-head comparison of Animas, Medtronic MiniMed and Roche

<table>
<thead>
<tr>
<th>Device</th>
<th>Number of meals</th>
<th>Preprandial (mg/dL)</th>
<th>2-h postprandial (mg/dL)</th>
<th>6-h postprandial (mg/dL)</th>
<th>Bolus recommendation at 2h</th>
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<tbody>
<tr>
<td>Roche IDS</td>
<td>45</td>
<td>110.8 ± 31.4</td>
<td>231.6 ± 37.8</td>
<td>120.8 ± 34.7</td>
<td>1.45 ± 0.92</td>
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<td>Animas</td>
<td>45</td>
<td>108.3 ± 31.2</td>
<td>226.4 ± 38.2</td>
<td>126.7 ± 47.4</td>
<td>1.26 ± 0.96</td>
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<tr>
<td>MiniMed</td>
<td>22</td>
<td>127.0 ± 39.1</td>
<td>260.3 ± 32.3</td>
<td>154.6 ± 37.0</td>
<td>1.04 ± 0.77</td>
</tr>
</tbody>
</table>

Data are mean ± SD values.

Hypo Events

- Roche IDS: 2
- Animas: 2
- MiniMed: 0

Zisser et al, *DT&T* 2010; 12:955
Considerations in the Settings for Insulin-on-Board Function in Bolus Calculators

\[
\text{Current glucose} - \text{Target glucose} = \text{Correction dose} - \text{Insulin on board} = \text{Recommended Insulin dose}
\]
Considerations in Calculating IOB

1. Insulin duration of action

Pharmacokinetic data (package inserts) is misleading about insulin action profile

Marked inter- and intra-individual variability

Other factors include:
- Insulin dose
- Temperature
- Exercise
- SC fat thickness

Considerations in Calculating IOB

2. Pump differences in insulin action curve

Driven by IP considerations and competitive marketing, little practical relevance

Primary consideration in selecting insulin duration of action is risk for hypoglycemia from dose stacking.

If priority is avoidance of hypoglycemia (e.g. hx of severe hypoglycemia, hypoglycemia unawareness) set duration longer:

- Reduces risk for stacking and hypoglycemia
- But may overcompensate for IOB, leading to under-dosing and failure to adequately correct
What Insulin Bolus Should the IOB Calculation Consider?

When calculating correction bolus:

**Approach #1:** Subtract out IOB from previous correction bolus only, or

**Approach #2:** Subtract out IOB from previous correction + carbohydrate bolus

Depends on type of carbohydrate load consumed:

**Approach #1** assumes carbohydrate-on-board at time correction dose is taken i.e. low glycemic index meal

**Approach #2** assumes NO carbohydrate-on-board at time correction dose is taken i.e. high glycemic index meal

In practice: #2 will lead to more aggressive reduction in correction dose, protecting against hypoglycemia
QUESTION 2: What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for diabetes management?

1. While patients need to know the key elements in dose calculation, not realistic to expect most patients or clinicians to understand complexities and nuances of IOB calculations

2. In practice, important to know whether particular IOB settings are biased to aggressive vs cautious insulin delivery
QUESTION 2: What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for diabetes management?

3. Impossible to perform scientifically-valid studies to evaluate bolus calculators that would be generalizable to real-world use. Experimental challenges include:

- Appropriate attention control group
- Difficulty in isolating benefit of bolus calculator from other variables (such as carb counting skills) that are determinants of success in using the technology
- Appropriate characterization of study population (likely benefit from/need for bolus calculator depend on diabetes self-management mastery)
- Inherent bias of algorithms related to food choices
QUESTION 3: How can FDA foster both innovation and safety of insulin dose calculators intended for use by healthcare practitioners?

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Break down the questions:
How can FDA foster both innovation and safety of bolus calculators?
QUESTION 3: How can FDA foster both innovation and safety of insulin dose calculators intended for use by healthcare practitioners?

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Break down the questions:
How can FDA foster both innovation and safety of bolus calculators?
How does intended use of bolus calculators by healthcare practitioners and patients differ?
How Does Intended Use of Bolus Calculators by Health Care Practitioners and Patients Differ?

- Healthcare practitioners and patients use bolus calculators in different environments
  - Challenges and priorities in diabetes management in medical facilities are different to home/outpatient setting
- In outpatient diabetes management, precedence is on flexibility in dosing with deviation from prescribed boluses to account for other factors (such as activity, alcohol, etc), whereas in the hospital the focus is on close adherence to prescribed medication dosing protocols
- In ICU: fewer confounding factors affecting glucose (food intake, exercise) + faster insulin action time (iv)
  - Tight glycemic control easier to accomplish with less need for deviation from prescribed protocols
- Scientific validity of dosing algorithms used by health care practitioners in ICU can be evaluated much more readily than that of insulin bolus calculators used by patients in home environment

These differences need to be factored into regulatory requirements.
Bolus Calculator Tools: Today

Regulated Medical Devices

Smartphone Apps

Innovation, no regulation
Bolus Calculator Tools: Today

Regulated Medical Devices

Smartphone Apps

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<tbody>
<tr>
<td>Target rate</td>
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</tr>
<tr>
<td>Corrective factor</td>
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<tr>
<td>Carbohydrate factor</td>
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<table>
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<th>INPUT</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>98</td>
</tr>
<tr>
<td>Carb: grams</td>
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</tr>
<tr>
<td>Insulin</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Dangerous default settings

Innovation, no regulation
Bolus Calculator Tools: Today

- Regulated Medical Devices
- Smartphone Apps
  - Glucose data entry errors

Innovation, no regulation
Bolus Calculator Tools: Today

Regulated Medical Devices

Smartphone Apps

Finger slip: changes from mg/dl to mmol/l!

Innovation, no regulation
Bolus Calculator Tools: Tomorrow
Balancing Innovation and Safety

Regulated Medical Devices

Regulated Diabetes Data Management and Decision Support Platforms

Data Inputs
- Glucose
- Insulin
- Activity
- Food

Diabetes Management Apps: Software Validated

Smartphone Apps

Health
- Diabetes Personal Calculator
- Insulin Protocol
- EZ Insulin
- Insulin RX
- Rapid Calc
- GC E =
- IOB Calc
Concluding Comment
Different risk mitigation approaches and regulatory pathways are required for:

1) Software that operationalizes paper-based insulin dosing instructions, including algorithms, prescribed by HCPs in routine diabetes management versus

2) Software incorporating more sophisticated insulin delivery algorithms that automatically optimize insulin doses without HCP verification (such as AP)

Case 2) requires full clinical trials since HCP is not in the loop, whereas for Case 1) strict adherence of the software company to quality control, including extensive testing and usability studies with patients and HCPs, would be adequate
Thank you