Demystifying Insulin Pump Therapy

Jacobus van Dyk
Paediatric Endocrinologist.
WHY?
OBJECTIVE

- Determine if Intensive Therapy (CSII) reduces long-term complications associated with diabetes versus Conventional Therapy (MDI)

DESIGN

- 10 Year Study (n = 14041 patients)
- 2 Groups:
  - Conventional Therapy (1-2 injections/day)
  - Intensive Therapy ($\geq$3 injections/day or Pump)
RESULTS

- Intensively treated patients achieved a mean A1C of 7.3%, compared with 9.1% for conventionally treated patients.
- Good control of blood glucose levels reduces the risk of microvascular complications.
EDIC (Epidemiology of Diabetes Interventions and Complications)

- **OBJECTIVE**
  - 4 years after completion of DCCT
  - Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus
EDIC (Epidemiology of Diabetes Interventions and Complications)

RESULTS

- 4 years after completion of DCCT
EDIC (Epidemiology of Diabetes Interventions and Complications)

- **RESULTS**
  - EDIC Supports Early Adoption of Intensive Therapy
  - Metabolic Memory / Legacy Effect

![Cumulative Progression of Retinopathy](image)

**Metabolic Memory**
1. Prior glucose control has an effect on ongoing risk of complications

<table>
<thead>
<tr>
<th>Years</th>
<th>No. Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional</td>
</tr>
<tr>
<td>1</td>
<td>169</td>
</tr>
<tr>
<td>2</td>
<td>203</td>
</tr>
<tr>
<td>3</td>
<td>220</td>
</tr>
<tr>
<td>4</td>
<td>581</td>
</tr>
<tr>
<td>5</td>
<td>158</td>
</tr>
<tr>
<td>6</td>
<td>192</td>
</tr>
<tr>
<td>7</td>
<td>200</td>
</tr>
</tbody>
</table>

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People with diabetes choose pumps for:

- A convenient and more normal lifestyle
- Flexibility in when and how much to eat
- Improved matching of insulin delivery to the body’s variable needs
- Less hypoglycaemia and hypoglycaemia awareness
People with diabetes choose pumps for:

- Assistance with calculations.
- Data tracking required to achieve optimal control
- Improved balancing of exercise with insulin
- Freedom to travel or to perform shift work
Health professionals recommend pumps for:

- Sub-optimal control
- Dawn Phenomenon with elevated fasting blood sugars
- Frequent or severe hypoglycaemia or hypoglycaemia unawareness
- Night time hypoglycaemia
- Low insulin requirement
Health professionals recommend pumps for:

- Frequent travel & variable work schedule
- Intensive exercise or athletics
- Tracking insulin doses, carbs, glucose levels – critical to control
- Reminders
Health professionals recommend pumps for:

- Preventing, delaying or reversing complications
- Improving control during puberty
- Frequent DKA / hospitalizations
- Gastroparesis
Is a pump better than multiple injections?

Better insulin delivery

- With multiple injections the pump mimic the basal or back ground insulin
- Bolus doses to cover meals
- Correction boluses to correct BG

More convenience and flexibility

- Weekends and holidays.
- Prevent insulin stacking.
Is a pump better than multiple injections?

**Greater precision**
- Increments of 0.025 units (twenty five thousands of a unit) – prevent critical low BG levels

**More reliable insulin action**
- Specially the Lente, NPH and Ultra Lente insulin – 25% variability. New analogues better.
- Only with pump therapy basal delivery can be matched to needs like Dawn Phenomenon, changing waking or work hours or with strenuous exercise.
Is a pump better than multiple injections?

**Easier problem solving**
- Only ultra short acting insulin in the pump
- Easier to separate the basal and bolus effect

**Less Hypoglycaemia with lower HbA1c**
- Specially so with sensor augmented pump therapy
- Less hypoglycaemia unawareness.
Drawbacks to pumping

It is a mechanical device!

- Pumps use small computers to deliver sophisticated doses of insulin.
- Therefore requires a conscientious user to go through a learning curve in order to make it work properly.

A pump is not the answer for everyone!
OBJECTIVES

This meta-analysis aimed to evaluate the clinical effectiveness of CSII therapy in reducing severe hypoglycaemia frequency and HbA1c levels, as compared to MDI therapy.

DESIGN

- Meta-analysis of 22 RCTs or B/A studies
- CSII vs MDI
- CSII therapy duration between 6 to 48 months
- 1414 subjects with Type 1 diabetes

RESULTS

SH significantly and markedly reduced during CSII compared with MDI

**FIGURE 1**: Rate ratios of severe hypoglycaemic events between CSII and MDI

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RESULTS

- Significantly better control of HbA1c on CSII compared with MDI
- The mean HbA1c level was 0.62% lower with CSII therapy compared to MDI therapy (0.72% and 0.21% in B/A studies and RCTs, respectively)

**FIGURE 2: Mean difference in HbA1c levels between CSII and MDI**

OBJECTIVES

• This study aimed to evaluate the long-term clinical effectiveness of CSII therapy in improving glycaemic control and reducing severe hypoglycaemia and DKA hospitalisation as compared to insulin injection therapy in children with Type 1 diabetes.

DESIGN

• Observational, retrospective case control study
• CSII versus MDI
• 7 year duration
• 345 children (aged up to 28 years)
LONG TERM BENEFIT OF CSII IN CHILDREN COMPARED TO MDI

RESULTS

• The rate of severe hypoglycaemia was reduced by 51% in the CSII group from baseline.
• In comparison, the rate of severe hypoglycaemia increased by 50% in the injection group.

TO UNDERSTAND THE SETTINGS AND DELIVERING OF INSULIN, WE HAVE TO GO BACK TO THE NORMAL PHYSIOLOGY OF INSULIN AND CARBOHYDRATE METABOLISM
Metabolic regulation

Rates of energy intake and output for a person during a typical day
Metabolic regulation

Intake of nutrients

Delivery of energy as required

Varying from moment to moment and from tissue to tissue

In a pattern which have no relationship to the pattern of intake
Historically diabetes was viewed as a relative or absolute Insulin deficiency.

**Glucoregulatory Hormones**

- Insulin - pancreas β-cell
- Glucagon – pancreas α-cell
- Amylin - pancreas β-cell
- GLP-1 – L-cells of the intestine
- Other:
  - Growth hormone, Epinephrine
  - Cortisol
  - GIP – L-cells
Plasma glucose concentration is the function of the rate of glucose entering the circulation balanced by the rate of glucose removal from the circulation.
Factors affecting blood glucose levels

- Urinary glucose excretion
- Hepatic glucose production
- Intestinal glucose absorption
- Cellular glucose utilization
Glucose transport

Tissue that are freely permeable to glucose:

• Brain, renal medullae, RBC and WBC
• They need a constant supply for minute to minute needs

However most tissue are highly dependent upon INSULIN
Actions of Insulin

- To lower blood levels of Glucose, Fatty acids, Amino acids
- To be stored as Glycogen, Triglycerides, Protein
- Suppresses Glucagon
Actions of Glucagon

- Stimulates the breakdown of stored liver glycogen
- Promotes hepatic gluconeogenesis
- Promotes hepatic ketogenesis
Actions of Amylin

Supresses postprandial glucagon secretion

Slows gastric emptying

Reduces food intake and body weight
Actions of GLP-1

- Enhances glucose-dependent insulin secretion
- Suppresses postprandial glucagon secretion
- Slows gastric emptying
- Reduces food intake and body weight
Insulin action

Figure 5.11 (a) The biphasic glucose-stimulated release of insulin from pancreatic islets. (b) The glucose-insulin dose-response curve for islets of Langerhans.
Insulin action
Glucose transporter proteins

**GLUT-1**
- Involved in basal and non-insulin-mediated glucose uptake

**GLUT-2**
- Important in the islet B cell

**GLUT-3**
- Non-insulin uptake in the brain

**GLUT-4**
- Responsible for insulin-mediated glucose uptake in muscle, and adipose tissue
Figure 5.12 The mechanism of glucose-stimulated insulin secretion from the β cell. The structure of the KATP channel is shown in the inset.

Figure 5.13 The classic experiment illustrating the incretin effect in normal subjects who were studied on two separate occasions. On one occasion, they were given an oral glucose load and on the second occasion an IV glucose bolus was administered in order to achieve identical venous plasma glucose concentration-time profiles on the two study days (left panel). The insulin secretory response (shown by C-peptide) was significantly greater after oral compared with IV glucose (right panel). Adapted from Nauck et al. J Clin Endocrinol Metab 1996, 81: 492-498.
Figure 5.17 (a) The structure of a typical glucose transporter (ILDL). (b) The intramembrane domains pack together to form a central hydrophilic channel through which glucose passes.

Figure 5.18 Insulin regulation of glucose transport into cells.
The Insulin Pump

- Basal
- Bolus
The insulin pump

**BASAL INSULIN DELIVERY**

- 40-50% of total daily insulin
- Overnight basal:
  - Can you go to bed with BG 5,0-6,7 mmol and wake up with a target reading?
- Daytime basal:
  - With a target BG before a meal, can you skip that meal and have a BG rise no more than 0,85 mmol or fall no more than 1,7 mmol
Basal insulin requirement – age difference
The Insulin Pump

Bolus

- Meal bolus:
  - Patient should be able to do carb counting
  - CARB RATIO: 350-450 ÷ Total daily dose of insulin
- Correction bolus
  - The insulin necessary to correct the BG to at least 6 mmol/L
  - Correction factor: 100 ÷ Total daily dose of insulin

Total meal bolus: Meal bolus + Correction Bolus
CSII – Three modes to deliver insulin

- Normal
- Dual-wave
- Square-wave
Insulin Pump

Complex bolus:

• Bolus necessary with high fat and high protein meal.
• Dual wave: dose is split in % given immediately and the rest over 3 – 6 hours.
PROTEIN AND FAT MEAL CONTENT INCREASE INSULIN REQUIREMENT IN CHILDREN WITH TYPE 1 DIABETES – ROLE OF DURATION OF DIABETES

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b Life Groenkloof Hospital, Pretoria, 0181, South Africa
Pańskowska et al: Quantified meal insulin based on all macronutrients (carbohydrate fat and protein CFP counting.

- Increased risk for early post-prandial hypoglycemic events
- Challenging to implement in the pediatric population


- Indicated that we need randomized controlled trials, aimed at developing methods to better manage post-prandial hyperglycaemia.
The aim of this study was to determine the post-prandial glycemic response and total insulin need for mixed meals with known, constant carbohydrate content but different fat and protein contents, using insulin pump therapy and CGM in children with type 1 diabetes.
Study design

A home-based, cross-over, randomized controlled trial

• Optimal basal insulin rates, carbohydrate ratios and sensitivity factors were revised and adjusted before enrolment. (Had to remain unchanged until after data collection)

• Two meals were consumed at dinner time (18:00) under parental supervision at least a day apart and within one month.

• Participants maintained their normal habitual activity.

• Study meals could only be taken on days 2 -5 of the sensor lifespan

• All participants used rapid acting insulin Novorapid.
Test meals

The macronutrient content was calculated as follows:

- Total daily energy requirement for each participant was individually calculated using age, weight and gender specific WHO energy expenditure recommendation.
- Total carbohydrate per day was calculated at 50% of total energy, since 50 -55% is recommended for children with type 1 diabetes. -ISPAD
- Of the total daily carbohydrates, 25% was allocated to each meal.
Test meals

The macronutrient content was calculated as follows:

- The amount of carbohydrates for both meals was kept constant in order for the LFLP meal to be used as the control for the HFHP meal.
- The fat and protein content per meal, calculated as percentage energy, were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Carbohydrate</th>
<th>FAT 25%</th>
<th>PROTEIN 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFLP</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFHP</td>
<td>CARBOHYDRATE 40%</td>
<td>35%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Outcome measures
Medtronic Carelink Software professional version.

- Peak sensor glucose value post meal
  - Maximum post meal glucose excursion above 6 mmol/L

- Time to peak sensor glucose excursion
  - Time it took following consumption of meal, to reach the maximum post-meal glucose excursion.

- Time of first and largest correction bolus

- Total correction bolus
  - Total additional insulin

- Total amount of insulin needed for the meal
  - Meal bolus and correction bolus

- Additional insulin required – correction bolus as percentage of total bolus
Outcome measures
Medtronic Carelink Software professional version.

- Area under the response curve (AUC) (≥ 8 mmol/L) post meal calculated using the trapezoidal method

- Duration of elevated post-prandial glucose

  - Total time of elevated post-prandial glucose spent above 6 mmol/L
Table 2: Insulin dosage and sensor glucose response curve comparisons between test meals

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>LFLP</th>
<th>HFHP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total correction insulin (units)</td>
<td>0.15 (0 ; 0.53)</td>
<td>1.2 (0.48 ; 2.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total meal insulin (units) ^a</td>
<td>2.70 (1.68 ; 5.80)</td>
<td>3.48 (2.43 ; 7.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Additional insulin required (%) ^b</td>
<td>11.3 ± 5.36</td>
<td>31.1 ± 16.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time of 1st correction bolus (min post-meal)</td>
<td>352 ± 204</td>
<td>352 ± 170</td>
<td>0.81</td>
</tr>
<tr>
<td>Time of largest correction bolus (min post-meal)</td>
<td>399 ± 192</td>
<td>420 ± 160</td>
<td>0.7</td>
</tr>
<tr>
<td>Basal suspend duration (min)</td>
<td>86.1 ± 79.9</td>
<td>53.3 ± 53.9</td>
<td>0.052</td>
</tr>
<tr>
<td>Duration of elevated post-prandial glucose (min) ^d</td>
<td>185 ± 124</td>
<td>364 ± 142</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak sensor glucose value post-meal (mmol/L)</td>
<td>9.22 ± 2.09</td>
<td>10.3 ± 2.77</td>
<td>0.14</td>
</tr>
<tr>
<td>Time to peak sensor glucose value (min post-meal)</td>
<td>233 ± 204</td>
<td>342 ± 178</td>
<td>0.056</td>
</tr>
<tr>
<td>Sensor glucose peak excursion ^c</td>
<td>3.42 ± 1.94</td>
<td>4.29 ± 2.77</td>
<td>0.18</td>
</tr>
<tr>
<td>AUC (above 8 mmol/L)</td>
<td>46.3 (0 ; 211)</td>
<td>198 (11.7 ; 505)</td>
<td>0.02</td>
</tr>
<tr>
<td>Occurrence of hypoglycaemic events n (%)</td>
<td>7 (32)</td>
<td>1 (0.05)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

^a food bolus and correction boluses; ^b correction bolus expressed as % of initial food bolus; ^c (difference between peak sensor glucose value and target of 6 mmol/L); AUC – area under the sensor glucose curve, ^d total time of elevated post-prandial glucose spent above 6 mmol/L. Data reported as mean ± SD or median (25th ; 75th percentile) depending on normality.
Figure 1  Blood glucose levels before (Time 0h) and after (Time 0.5 – 10h) intervention

- High fat, high protein meal;  ▲ - Low fat, low protein meal
* - significant difference between the two meals (p < 0.05) at the respective time points
Meal bolus (T 0h) and correction insulin (T 2 - 10h)

- ■ – High fat, high protein meal; ▲ - Low fat, low protein meal
- * - significant difference between the two meals (p < 0.05)
This study highlights the additional insulin needed for a typical mixed meals in children with type 1 diabetes and shows that all macronutrients require insulin.

With the addition of each 1 gram of fat requiring double the amount of correction insulin compared to each gram of protein.
For the first time, duration of diabetes (regardless of age) is shown to be strongly associated with post-prandial hyperglycemia.
Insulin Pump

Trouble shooting:

- Exercise
- Low Blood Glucose
- High Blood Glucose
Insulin Pump

Other setting:

• Active insulin time
• Bolus increment
• Basal increment
• Maximum bolus
• Maximum basal
• Temp basal type
36% of parents feel they argue with their child on a daily basis about device use.

SOURCE: COMMON SENSE MEDIA
Sensor Augmented insulin Pump therapy

• Major advancement is the predicted low glucose suspend
### Bolus Events

<table>
<thead>
<tr>
<th>Bolus Event</th>
<th>Time</th>
<th>Bolus Type</th>
<th>Glucose (mmol/L)</th>
<th>Carb</th>
<th>BG (mmol/L)</th>
<th>BG Target Setting (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>01:29 AM</td>
<td>Normal</td>
<td>7.4</td>
<td>-</td>
<td>7.9</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>2</td>
<td>06:37 AM</td>
<td>Normal</td>
<td>6.8</td>
<td>-</td>
<td>6.3</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>3</td>
<td>07:19 AM</td>
<td>Normal</td>
<td>7.6</td>
<td>-</td>
<td>7.4</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>4</td>
<td>08:03 AM</td>
<td>Normal</td>
<td>7.4</td>
<td>-</td>
<td>6.8</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>5</td>
<td>10:02 AM</td>
<td>Normal</td>
<td>7.4</td>
<td>-</td>
<td>7.4</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>6</td>
<td>11:31 AM</td>
<td>Normal</td>
<td>7.3</td>
<td>-</td>
<td>7.4</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>7</td>
<td>01:37 PM</td>
<td>Normal</td>
<td>7.4</td>
<td>-</td>
<td>7.4</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>8</td>
<td>02:24 PM</td>
<td>Normal</td>
<td>7.4</td>
<td>-</td>
<td>7.4</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>9</td>
<td>08:09 PM</td>
<td>Normal</td>
<td>7.4</td>
<td>-</td>
<td>7.4</td>
<td>5.5 - 6.5</td>
</tr>
<tr>
<td>10</td>
<td>09:45 PM</td>
<td>Normal</td>
<td>7.4</td>
<td>-</td>
<td>7.4</td>
<td>5.5 - 6.5</td>
</tr>
</tbody>
</table>

### Statistics

<table>
<thead>
<tr>
<th></th>
<th>09/28</th>
<th>09/26 - 10/09</th>
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</thead>
<tbody>
<tr>
<td>Avg BG (mmol/L)</td>
<td>9.6</td>
<td>9.4 ± 1.4</td>
</tr>
<tr>
<td>BG Readings</td>
<td>8</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.5/day</td>
</tr>
<tr>
<td>Readings Above Target</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Readings Below Target</td>
<td>25%</td>
<td>3%</td>
</tr>
<tr>
<td>Sensor Avg (mmol/L)</td>
<td>9.1 ± 2.5</td>
<td>9.3 ± 2.6</td>
</tr>
<tr>
<td>Avg AUC &gt; 7.8 (mmol/L)</td>
<td>1.82</td>
<td>1.6 ± 1.32h</td>
</tr>
<tr>
<td>Avg AUC &lt; 3.9 (mmol/L)</td>
<td>0.00</td>
<td>0.00 ± 1.5h</td>
</tr>
<tr>
<td>Daily Carbs (g)</td>
<td>79</td>
<td>90 ± 19</td>
</tr>
<tr>
<td>Carbs/Bolus Insulin (g/U)</td>
<td>10.5</td>
<td>10.4</td>
</tr>
<tr>
<td>Total Daily Insulin (U)</td>
<td>11.85</td>
<td>19.07 ± 1.7</td>
</tr>
</tbody>
</table>
**MINIMED™ 640G WITH SMARTGUARD™ TECHNOLOGY HYPOGLYCAEMIA REDUCTION IN PAEDIATRICS**

**OBJECTIVES** To evaluate the effectiveness of SmartGuard suspend before low feature in reducing hypoglycaemia, compared to conventional SAP therapy, in a paediatric population.

**RESULTS**

Reduction in Hypoglycaemia:

<table>
<thead>
<tr>
<th>Area Under the Curve</th>
<th>Time spent</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before/After</td>
<td>SmartGuard ON vs OFF</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td>24 subjects</td>
<td>Type 1</td>
</tr>
<tr>
<td></td>
<td>Aged 3-17</td>
<td></td>
</tr>
</tbody>
</table>

Best results, with no hyperglycaemic rebound, when no intervention with SmartGuard.

76.8% avoidance of low limit following SmartGuard suspension events.

**INSIGHT** SmartGuard significantly reduces hypoglycaemia in paediatrics, for optimal result patients should be educated to trust the technology and ‘let SmartGuard do the work’.

**REFERENCE**
Biester T. et al. “Let the Algorithm Do the Work”: Reduction of Hypoglycemia Using Sensor- Augmented Pump Therapy with Predictive Insulin Suspension (SmartGuard) in Pediatric Type 1 Diabetes Patients.

OBJECTIVES The study aimed to evaluate the clinical effectiveness of SAP therapy with the LGS feature, as compared to SAP without LGS feature, on nocturnal hypoglycaemia and HbA1c levels in patients with documented nocturnal hypoglycaemia.

RESULTS The mean AUC for nocturnal hypoglycaemic events was 38% lower in the LGS Group than in the Control Group.

INSIGHT Low Glucose Suspend can reduce by 38% the mean AUC of nocturnal hypoglycemia without increasing HbA1c vs SAP.
THE CLOSE FUTURE
New insulin

**Fast-acting Insulin Aspart**

- By adding L-arginine and niacinamide
  - L-arginine – stabilising agent
  - Niacinamide – accelerated initial absorption

**Studies published in adults - paediatric studies ongoing**
GLP-1

? Use in type 1 diabetes
MINIMED™ 670G SYSTEM WITH SMARTGUARD™ TECHNOLOGY
COMPARING GLUCOSE REQUIREMENTS OVER 4 DIFFERENT NIGHTS

EACH DAY AND NIGHT, INSULIN NEEDS VARY

By constantly adapting to real-time insulin needs, SmartGuard™ technology may deliver very different basal rates each day and night – helping patients stay in a healthy glucose range.\(^1,2\)