How to improve glucose variability of patients with unstable type 1 diabetes?

Chisinau – October 10, 2014

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THE TYPE 1 DIABETES PARADIGM:

TYPE 1 DIABETES IS AN UNSTABLE SITUATION BY ITSELF.

M.-C. Vantyghem, M. Press

This « unstability » (glucose variability) is associated with loss of endogen insulin secretion.
How to improve GV of patients with unstable TD1?
GV is associated with loss of endogenous insulin secretion


Bott U et al. Predictors of glycaemic control in T1D patients after participation in an intensified treatment and teaching programme (1994).
Glucose variability prevents reaching glycemic targets without experiencing any hypoglycemic events.

How to improve GV of patients with unstable TD1?

GV is associated with hypoglycemia.

Failure of simple titration algorithms.

Glargine 12U + 2U
Glycemic control is limited by the barrier of hypoglycemia* (through glucose variability)

Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes


Determinants of glycaemic control in T1D during intensified therapy with MDI or CSII: importance of blood glucose variability.


* Philip E. Cryer
How to improve GV of patients with unstable TD1?

The “obvious” causes of Glucose Variability

<table>
<thead>
<tr>
<th>Psychosocial factors (74%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malabsorption</strong></td>
</tr>
<tr>
<td>- Coeliac disease</td>
</tr>
<tr>
<td>- Fat malabsorption</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>- Alcohol abuse</td>
</tr>
<tr>
<td>- Antipsychotic drugs (Quetiapine)</td>
</tr>
<tr>
<td><strong>Autonomic neuropathy</strong></td>
</tr>
<tr>
<td>- Gastroparesis</td>
</tr>
<tr>
<td>- Hypoglycemic unawareness</td>
</tr>
<tr>
<td><strong>Subcutaneous causes</strong></td>
</tr>
<tr>
<td>- Defective insulin absorbtion</td>
</tr>
<tr>
<td>- Accelerated degradation</td>
</tr>
<tr>
<td>- Insulin allergy</td>
</tr>
<tr>
<td><strong>Defects of counter-regulatory hormones</strong></td>
</tr>
<tr>
<td>- Adrenal insufficiency</td>
</tr>
<tr>
<td>- Hypopituitarism</td>
</tr>
<tr>
<td>- Glucagon deficiency (eg. Post-pancreatectomy)</td>
</tr>
<tr>
<td>- Abnormal GH regulation</td>
</tr>
<tr>
<td><strong>Auto-antibodies</strong></td>
</tr>
<tr>
<td>- Anti-insulin</td>
</tr>
<tr>
<td>- Anti-insulin receptor</td>
</tr>
</tbody>
</table>

- Human (patient) errors
  - missed insulin injections (consciously or not)
  - missed / false SMBG data
  - wrong meal insulin bolus
  - anorexia / bulimia
  - fear of hypoglycemia
  - Crystallized (slow acting) insulin not well mixed
  - Injections in lipodystrophic area ...

How to improve GV of patients with unstable TD1?

Variability Shrinker

- Intensive glucose Self-monitoring
- Carbohydrate Counting
- Insulin Pump
- Continuous Glucose Monitoring
How to improve GV of patients with unstable TD1?

Documentation of GV
How to improve GV of patients with unstable TD1?

Documentation of GV
How to improve GV of patients with unstable TD1?

Basal insulins pharmacodynamics in T1D: Partly the cause of the “intrinsic” glucose variability

GIR, glucose infusion rate

How to improve GV of patients with unstable TD1?

Portable insulin pump, currently used

Continuous Subcutaneous Insulin Infusion (rapid analog).
Pharmaco kinetics and -dynamics of s.c. Injection of Long-Acting Glargine, NPH, and Ultralente Human Insulin and CSII of Insulin Lispro


**Low inter-patient variability**

Mean ± SE of Standard Deviation

Intersubject variability of plasma glucose and insulin concentrations and GIR from the SDs of the 24 time points of the studies after SC injection and after CSII.
How to improve GV of patients with unstable TD1?
Adaptability of basal insulin rate

Characteristics of basal insulin requirements by age and gender in Type-1 diabetes patients using insulin pump therapy.


You get what you ask for!

Basal insulin needs are different from individuals and are not the same along the day.
### HbA1c outcome: Review of meta-analyses

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Reference</th>
<th>N</th>
<th>Type</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pickup JC, Mattock MB, Kerry S.</td>
<td>BMJ 2002;324:705-708</td>
<td>600</td>
<td>RCTs</td>
<td>-0.44%</td>
</tr>
<tr>
<td>Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R.</td>
<td>Diabetes Care 2003;26:1079–87</td>
<td>1547</td>
<td>Prosp.</td>
<td>-0.95%</td>
</tr>
<tr>
<td>Retnakaran R, Hochman J, DeVries JH et al.</td>
<td>Diabetes Care 2004;27:2590–96</td>
<td>139</td>
<td>RCTs</td>
<td>-0.35%</td>
</tr>
<tr>
<td>Jeitler K, Horvath K, Berghold A, et al.</td>
<td>Diabetologia 2008;51:941–951</td>
<td>908</td>
<td>RCTs</td>
<td>-0.40%</td>
</tr>
<tr>
<td>Pickup JC, Sutton AJ.</td>
<td>Diabet Med 2008;25:765–774</td>
<td>1414</td>
<td>RCTs* Bef/Aft*</td>
<td>-0.21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.72%</td>
</tr>
<tr>
<td>Fatourechi MM, Kudva YC, Murad MH et al</td>
<td>JCEM 2009;94:729–740</td>
<td>669</td>
<td>RCTs</td>
<td>-0.20%</td>
</tr>
<tr>
<td>Misso ML, Egberts KJ, Page M, O’Connor D, Shaw J.</td>
<td>Cochrane Datab 2010:CD005103</td>
<td>976</td>
<td>RCTs</td>
<td>-0.30%</td>
</tr>
<tr>
<td>Monami M, Lamanna C, Marchionni N, Mannucci E.</td>
<td>Acta Diabetol 2010;47 (S1):77–81</td>
<td>883</td>
<td>RCTs</td>
<td>-0.30%</td>
</tr>
</tbody>
</table>

*Only studies with rate of severe hypoglycaemia during MDI > 10 episodes/100 patient years*
HbA1c outcome: The impact of baseline A1c!

Glucose Variability Assessed by LBGI Is Predictive of Hypoglycemic Events in Patients With T1D Switched to CSII
Crenier L et al. Diabetes Care 2013; 36(8):2148-2153

Severe hypoglycaemia and glycaemic control in T1D: Meta-analysis of MDI compared with continuous subcutaneous insulin infusion
Pickup JC, Sutton AJ. Diabetic Medicine 2008; 25: 765-74

How to improve GV of patients with unstable TD1?
The role of insulin pump
How to improve GV of patients with unstable TD1?
The role of insulin pump

Hypoglycemia outcome : meta-analyses

<table>
<thead>
<tr>
<th>Meta-analysis</th>
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<th>Type</th>
<th>Hypoglycémies</th>
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<td>Pickup JC, Mattock MB, Kerry S.</td>
<td>BMJ 2002;324:705-708</td>
<td>600</td>
<td>RCTs</td>
<td>↓ SD</td>
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<td>Misso ML, Egberts KJ, Page M, O’Connor D, Shaw J.</td>
<td>Cochrane Datab 2010:CD005103</td>
<td>976</td>
<td>RCTs</td>
<td>↓ (SH)</td>
</tr>
</tbody>
</table>

*Only studies with rate of severe hypoglycaemia during MDI > 10 episodes/100 patient years
Hypoglycemic events rate is function of glucose variability

But ... what are the best indices?

Crenier L, unpublished data
Rodbard D. *Diabetes Technology Ther* 2012;14: 868-76

<table>
<thead>
<tr>
<th>R²</th>
<th>Mean</th>
<th>100%</th>
<th>53%</th>
<th>7%</th>
<th>17%</th>
<th>20%</th>
<th>32%</th>
<th>32%</th>
<th>18%</th>
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<tbody>
<tr>
<td>R²</td>
<td>SD</td>
<td>53%</td>
<td>100%</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
<td>0%</td>
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<tr>
<td>R²</td>
<td>CV</td>
<td>2%</td>
<td>33%</td>
<td>30%</td>
<td>36%</td>
<td>30%</td>
<td>25%</td>
<td>29%</td>
<td>18%</td>
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<tr>
<td>R²</td>
<td>Mage</td>
<td>39%</td>
<td>84%</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>R²</td>
<td>MODD</td>
<td>52%</td>
<td>85%</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
<td>4%</td>
<td>1%</td>
<td>1%</td>
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<tr>
<td>R²</td>
<td>GRADE</td>
<td>79%</td>
<td>75%</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>R²</td>
<td>CONGA-1</td>
<td>30%</td>
<td>64%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>R²</td>
<td>CONGA-4</td>
<td>42%</td>
<td>86%</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>R²</td>
<td>LBGI</td>
<td>35%</td>
<td>0%</td>
<td>48%</td>
<td>58%</td>
<td>58%</td>
<td>68%</td>
<td>68%</td>
<td>34%</td>
</tr>
<tr>
<td>R²</td>
<td>HBGI</td>
<td>95%</td>
<td>64%</td>
<td>3%</td>
<td>9%</td>
<td>11%</td>
<td>19%</td>
<td>19%</td>
<td>11%</td>
</tr>
<tr>
<td>R²</td>
<td>BGRI</td>
<td>74%</td>
<td>74%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>3%</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

R² (Pearson) computed on 41 CGM recordings from T1D and T2D patients
How to improve GV of patients with unstable TD1? 
The role of insulin pump

Glucose Variability on insulin pump
Expected CV reduction is function of baseline CV

Correlation of change in CV on Continuous Subcutaneous Insulin Infusion (CSII) and baseline CV.

Lytrivi M & Crenier L. P1004; EADS 2014, Vienna.

Crenier L et al. Diabetes Care 2013; 36(8):2148-2153
Mean of hypoglycemic events did not change globally in our cohort. But the mean might hide subgroups*!

* «The average person has one testicle and one ovary» (Unknown philosopher)
How to improve GV of patients with unstable TD1?
The role of insulin pump

Baseline LBGI predicts Δ Hypoglycemia
(Multivariate analysis)

Δ Hypoglycemia is the difference in number of hypoglycemic events<60 mg/dL (3.3 mmol/L) on CSII vs. MDI, documented from 1-month SMBG data.
Low Blood Glucose Index

Function of the number and the depth of past hypoglycemic episodes

\[ F(G) = 1.509 \times \left[ \ln(G)^{1.084} - 5.381 \right] \]

\[ Rl(G) = 10 \times F(G)^2 \text{ si } F(G)<0, \text{ ou } Rl(G)=0 \]

\[ LBGI = \frac{1}{n} \sum_{i=1}^{n} \left[ Rl(G_i) \right] \]

Kovatchev BP (...) and Clarke W. Diabetes Care 1998; 21: 1870-1875
Optimal LBGI cutoff for predicting reduction of hypoglycemic events

LBGI value of 3.34 gives the best compromise of sensitivity, 70.8% (95% CI 48.9–87.4) and specificity, 73.1% (52.2–88.4).

The ROC curve for the subgroup of patients with persistent hyperglycemia had an AUC of 0.690 ± 0.113 (p=0.09)

The ROC curve for the subgroup of patients with frequent or severe hypoglycemia had an AUC of 0.85 ± 0.116 (P=0.0026). Sensitivity reached 75% (34.9–96.8) and specificity 100% (69.2-100)

Crenier L et al. Diabetes Care 2013; 36(8):2148-2153
How to improve GV of patients with unstable TD1? The role of insulin pump

Analysis by LBGI tertile: Outcomes

- **LBGI T1** (0.62-2.05)**
  - ΔHbA1C (%): -0.99†
  - ΔHypoglycemia (event/week): 1.14*

- **LBGI T2** (2.19-4.13)**
  - ΔHbA1C (%): -0.46*
  - ΔHypoglycemia (event/week): 0.42

- **LBGI T3** (4.18-9.34)**
  - ΔHbA1C (%): -0.23
  - ΔHypoglycemia (event/week): -0.85§

*P = 0.01 vs. MDI, †P = 0.00001 vs. MDI, §P<0.05 vs. MDI. Intertertile comparisons significant for mean A1C changes (P<0.014 by ANOVA, post hoc Tukey showing T3>T1) and changes in hypoglycemic events (P<0.0029 by Kruskal-Wallis, post hoc Mann-Whitney showing T3<T1). Errors bars are SEM. **Numbers in parentheses are the range of the tertile.

Crenier L et al. Diabetes Care 2013; 36(8):2148-2153
Conclusions

• Insulin pump decreases variability for patients with the highest baseline CV (>45%)

• Baseline LBGI is the best predictor of hypoglycemia outcome on insulin pump (cut off = 3.34)

• Those with the highest baseline LBGI get the greatest lowering of hypoglycemic events on CSII

• Those with the lowest LBGI get the greatest lowering of A1C on CSII, but with increasing of hypoglycemia
How to improve GV of patients with unstable TD1?
The role of insulin pump: clinical case

Baseline on MDI
- HbA1c: 7.4%
- CV: 59.7%
- LBGI: 6.16
- H50: 2.4 h/d

6 months on CSII
- HbA1c: 6.8%
- CV: 41.6%
- LBGI: 4.27
- H50: 1.9 h/d
How to improve GV of patients with unstable TD1?
The role of insulin pump

The Sensor Augmented Pump

Configuration ASPIRE Study (NEJM, 2013)
The role of SA insulin pump: ASPIRE Study

How to improve GV of patients with unstable TD1?
How to improve GV of patients with unstable T1D?
Artificial Pancreas

Leelarathna L et al. Critical Care 2013, 17:R159

Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial

- Laptop computer
- Navigator Companion
- Insulin Infusion Pump
- Dextrose Infusion Pump
- Intravenous cannula
- Navigator Transmitter and sensor

Figure 4 An example of the 48-hour closed-loop study. Darker red continuous line represents sensor glucose. Lighter red squares represent reference glucose measurements used for sensor calibration. Blue line represents insulin infusion. Thin red dashed lines indicate primary target. Dextrose infusion was not required in this study.

Glucose (mmol/L)

Number of subjects
- Local Protocol: 12
- Closed-loop: 12

Study Hour

0 4 8 12 16 20 24 28 32 36 40 44 48

12 11 11 11 10 11 11
How to improve GV of patients with unstable TD1?

Mulţumesc Pentru Atenţie!