Glucose Variability – A New Standard: how to measure it and why it is important

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Disclosures

• Research support: Eli Lilly
• Speaker’s fee: Dexcom Inc
At the conclusion of this presentation, the participant should be able to:

- Identify two harmful outcomes consistently associated with increased glucose variability
- Summarize the impact of lowering glucose variability in interventions trials performed so far
What is variability?

- It is not about the hypers
- It is not about the hypos
Outline

• Is there a relationship between glucose variability and microvascular damage in Type 1 diabetes, and how did the idea emerge?
• Is there a relationship between glucose variability and macrovascular damage in Type 2 diabetes?
• How to measure glycemic variability
• Back to the patient

Siegelaar, Endocrine Reviews 2010;31:171-82
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DCCT; risk of retinopathy per A1c stratum

Diabetes 1995;44:968-83 Figure 5
Hypothesis

If an HbA1c of 9% in the conventional group carries more risk than 9% in the intensive group, than it must be variability!
DCCT, glucose variability and microvascular damage

Kilpatrick et al. Diabetes Care 2006;29:1486-90
DCCT; risk of retinopathy per A1c stratum

Diabetes 1995;44:968-83 Figure 5
Retraction: Diabetes 2008;57:995-1001
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Preliminary Communication: Glucose Variability and oxidative stress in type 2 diabetes on OHA

Monnier JAMA 2006;295:1681
Glucose Variability and oxidative stress in type 2 diabetes on OHA

Monnier JAMA 2006;295:1681 and Diabetologia 2010;53:562
Siegelaar JDST 2011,5:1668-74
Monnier 5 years down the road

- 2006: 74% of the statistical variation in 8-iso’s explained by MAGE
- 2011: 15% of the statistical variation in 8-iso’s explained by MAGE, only in patients in very poor control
No correlation between glycemic variability and oxidative stress in Type 1 diabetes

Wentholt, Kulik, Michels, Hoekstra, DeVries. Diabetologia 2008;51:183-90
Monnier, Diabetologia 2010;53:562-71: no correlation in Type 1 diabetes
Associations Glucose Variability in Type 2 Diabetes with

- FMD IMT: unclear (Buscemi, DMed)
- Cognitive dysfunction: positive (Rizzo DC)
- Variability FBG, weight and pulse pressure associate with mortality (Zoppini, DMed)
- Z-score of CV risk: negative (Borg, Diabetologia)
- Mortality in patients with CHF (Dungan DMRR)
HEART2D: prandial vs basal insulin in post MI T2DM

Raz et al. Diabetes Care 2009;32:381
HEART2D: Glucose Variability less with prandial approach

Raz et al. Diabetes Care 2009;32:381
Mean Absolute Glucose change (MAG)

- Measures of glucose variability
  - Standard Deviation (SD)
  - Mage
  - Mean Absolute Glucose change (MAG) mmol/l/hr (|ΔBG|/hr)

Patient 1
- Mean glucose 7.5 mmol/l (135 mg/dl)
- SD 2.5 mmol/l (45 mg/dl)
- MAG 0.25 mmol/l/hr (4.5 mg/dl/hr)

Patient 2
- Mean glucose 7.5 mmol/l (135 mg/dl)
- SD 2.5 mmol/l (45 mg/dl)
- MAG 4.75 mmol/l/hr (85.5 mg/dl/hr)

Hermanides, Crit Care Med 2010 38:838–842
MAG on 7-point profile

Patient 1, mean glucose 8.1 mmol/l, SD 2.7 mmol/l, MAGE 3.0 mmol/l, MAG 0.25 mmol/l/h

Patient 2, mean glucose 8.1 mmol/l, SD 2.7 mmol/l, MAGE 3.0 mmol/l, MAG 0.50 mmol/l/h

Siegelaar et al. Diabetes Care 2011;34:855-7
HEART2D: Glucose Variability less with prandial approach

Siegelaar et al. Diabetes Care 2011;34:855-7
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How to measure variability?

- Range
- SD or CV
- M-value
- MAGE
- LBGI
- HBGI
- Lability Index
- ADRR
- CONGA
- And many more….
How to measure variability?

- Range
- SD or CV
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- Lability Index
- ADRR
- CONGA
- And many more...

High correlation between all these measures, e.g.
- MAGE & SD: r=0.88

Rodbard D, Diab Tech Ther 2009;11:551-65
Variability related to mean glucose

Correlation mean and SD: 0.56

Glycemic variability and ICU mortality

- Egi: 7,049 ICU patients
- Standard deviation (SD) is a predictor of ICU mortality and hospital mortality, independent of mean glucose

Egi et al. Anesthesiology, 2006
Variability in the ICU

Results: in-hospital mortality

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Range mean glucose (mmol/l)</th>
<th>Range MAG (mmol/l/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;6.93 (&lt;125 mg/dl)</td>
<td>&lt;0.39 (&lt;7 mg/dl)</td>
</tr>
<tr>
<td>2</td>
<td>6.93-7.60 (125-137 mg/dl)</td>
<td>0.39-0.60 (7-11 mg/dl)</td>
</tr>
<tr>
<td>3</td>
<td>7.61-8.91 (137-160 mg/dl)</td>
<td>0.61-0.87 (11-16 mg/dl)</td>
</tr>
<tr>
<td>4</td>
<td>&gt;8.91 (&gt;160 mg/dl)</td>
<td>&gt;0.87 (&gt;16 mg/dl)</td>
</tr>
</tbody>
</table>

MAG shows a stronger relation with mortality than SD

- difference in AUC of the ROC curve 5.4% (95% CI 3.0-7.7, $p<0.001$)

Hermanides, Crit Care Med 2010 38:838–842
How about MAGE?

• Changes < 1 SD are ignored

- Operator dependent
- Either upstrokes or downstrokes
- Excursion must be up and down > 1SD
- What is an excursion?

Baghurst, DTT 2011;13:295-301
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Variability predicts severe hypoglycemia in Type 1 diabetes

50 smbg in 2-3 wks, n=78, 6 mo follow-up severe hypo

Cox DJ, JCEM 1994;79:1659-62

Mean Number of Severe Hypoglycemic Episodes when Subject Below and Above the Median Split of the BG Variance

Mean Number of Severe Hypoglycemic Episodes when Subject Below and Above the Median Split of the Glycosylated Hemoglobin
Glucose variability on OAD predicts hypoglycemia on insulin

Qu Y, DT&T 2012; 14: 1008-12
Conclusions

• Glucose variability is not related to
  – Microvascular complications in Type 1 diabetes
  – Oxidative stress
• Variability is related to mean glucose
• Variability is related to ICU mortality
• MAG is a newly proposed standard measure for glucose variability
• Unpredictable glucose values are very disturbing for people with diabetes