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Medical Director, Banarsidas Chandiwala Institute of Medical Sciences
Chief Consultant, Centre for Diabetes & Lifestyle Diseases, Kalkaji, New Delhi

- Served API as Past President, Past Dean
- Editor in Chief – API Textbook of Medicine – 9th & 10th Editions
- Around 50 publications to his credit
- Orations, like Presidential Oration, Dean’s Oration, Rabindra Nath Tagore Oration
- Principal Investigator in many multicentric as well as multinational trials
- Advisory Committees of prestigious journals like Indian Heart Journal, JAPI, Journal of Clinical Diabetology, Indian Journal of Clinical Medicine etc.
Glycemic Variability:
The Third Component Of
The Dysglycemia In Diabetes
Currently Available Glucose Monitoring Tests

- Monitoring of Blood Glucose (MBG)
- Glycosylated Hemoglobin (HbA1c)
Glycemic Variability
Parameters of Glucose Measurement

**SMBG (Self Monitoring of Blood Glucose)**

- patterns provide day-to-day data used to select and manage glucose control programs and ultimately optimize A1C:
  - Provide a measure of the specific pharmacologic impact of oral treatment medications
  - Allow design and implementation of physiologic insulin-replacement programs

**A1C**

- provides the “big picture” - the average glycemia levels during previous 90 days (but is more heavily weighted by the most recent values) and correlates with end-organ impact
SMBG Does Not Give Patients the Whole Picture

Based on simulated data.
SMBG Does Not Give Patients the Whole Picture

Based on simulated data.
Glycosylated haemoglobin HbA1c

- Most widely used clinical test
- Measurement of blood glycated haemoglobin (also called haemoglobin A1C, glycohemoglobin and glycosylated haemoglobin [HbA1c], the average amount of A1C)
- Changes in a dynamic way
- Reflects the mean blood glucose concentration over the previous six to eight weeks

A1C value of 7% - 150mg/dl
A1C value of 9% - 210mg/dl
A1c is not perfect but over 31 yrs ...

<table>
<thead>
<tr>
<th>A1C</th>
<th>DCCT (T1D)</th>
<th>UKPDS (T2D)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 → 7%</td>
<td>8 → 7%</td>
</tr>
<tr>
<td>Retinopathy (Eye)</td>
<td>63%</td>
<td>17-29%</td>
</tr>
<tr>
<td>Nephropathy (Kidney)</td>
<td>54%</td>
<td>24-33%</td>
</tr>
<tr>
<td>Neuropathy (Nerve)</td>
<td>60%</td>
<td>-</td>
</tr>
</tbody>
</table>

A1c Shown to be linked to:

| Mortality              | (T2D) ✓   |
| Complications          | ✓         |
| ER visits / Hospital admissions | ✓ |
| Cost                   | ✓         |
| QOL                    | ✓         |
Over past 21 years since the end of DCCT (1993): The A1c is ..

- Gold Standard for judging level of glycaemic control
- Gold standard for judging risk of DM complications
Does A1C tell the whole story?

- A1C does not track glycaemic excursions
- 60% of glucose lows may not be revealed with SMBG alone*
- CGM identifies four times more serious glucose excursions than SMBG**

Key messages

- Marked PPG excursions and glucose fluctuations that occur despite HbA1c levels <7.0%.

- Fluctuations are not sufficiently reflected by changes in HbA1c.

- Thus relying mainly on HbA1c at a target level of 7.0% may be inadequate for timely therapeutic adjustments and reducing the risk of cardiovascular complications.
Glycemic variability looking beyond the HbA1c:

- Even at equal HbA1c, glycemic control can be extremely different in terms of absolute excursions.

Plasma glucose excursions following a meal are generally greater, last longer and are more variable in patients with type 2 diabetes compared with the normal population.
Glycemic Variability: Definition & Importance
Glycemic variability is a complex phenomenon that includes both intraday and interday variability.

- The intraday component corresponds to the within-day vertical glycemic fluctuations.

- The interday component is defined as day-to-day glucose variations.
So What Is The Significance of the Understanding of GV?

“...it suggests that different therapeutic strategies now in use should be evaluated for their potential to minimize glycemic excursion, as well as their ability to lower A1c.”

“...wider use of real-time continuous glucose monitoring in clinical practice would provide the required monitoring tool to minimize glycemic variability and superoxide overproduction.”

Measures of Glycemic Variability

- **MAGE** Mean Amplitude of Glycemic Excursion
- **SD** Standard Deviation
- **%CV** Coefficient of Variation
- **IQR** Inter-Quartile Range
- **MODD** Mean of Daily Differences
- **CONGAn** SD of Sequential Differences
- **MAG** Mean Absolute Glucose Rate of Change
- Stability of patterns from day to day
Reasons of Glycemic Variability

Diminished or absent glycemic auto regulation

OR

Shortfall of insulin availability are hypothesized to be the etiological factors for these glycemic bumps.

Indian J Endocrinol Metab. 2013 Jul-Aug; 17(4): 611–619
Variations are a Rule

- Glucose variations are not limited to postprandial hyperglycemic excursions.

- Such fluctuations are particularly marked in type 1 diabetes and to a lesser degree in patients with type 2 diabetes treated with insulin.

- Non-insulin-dependent patients can also experience such peak and trough patterns with acute glucose variations.

- Peaks are usually corresponding to maximum values after meals particularly mid-morning, while troughs are observed over inter-prandial periods.
Glycaemic Variability - Causes?

- **Insulin properties**
  - Profile of insulin - hexamers to monomers - Zinc/Protamine/pH
  - Insulin concentration
  - Insulin temperature
  - Injection sites
  - Depth of injection

- **Physician and user factors**
  - Wrong insulin choices
  - Wrong insulin doses
  - Erratic lifestyles without flexible regimen / dose adjustments

- **Endogenous factors**
  - SC blood flow
  - Age
  - Physical exercise
  - Obesity
  - Hypoglycaemia unawareness?
FACTORS ASSOCIATED WITH GREATER GLYCEMIC VARIABILITY

- Reduced β cell function
- Older age
- Renal impairment
- Anti-diabetic medication
- Polypharmacy
- Poor compliance with treatment
- Intake of food with higher glycemic index and/or glycemic load

G.V. Leads to Vascular Complication How?
Mechanism by Which Glycemic Variability LEADS to Complications

- Glycemic variability causes Diabetic Vascular Complications by two mechanisms:
  - Excessive protein glycation end products
  - Activation of oxidative stress in the causation of vascular complication
Growing Evidence

Cell culture studies by Ceriello showing increased inflammatory activation with glucose variability

Studies by Monnier showing increased oxidative stress with increases in MAGE

Studies by Katherine Esposito showing by reducing postprandial spikes inflammatory cytokines could be suppressed
Possible Mechanism

- Human umbilical vein endothelial cells (HUVECs) “exposed to intermittent hyperglycemia results in ROS overproduction, through a PKC-dependent activation …”

- This suggests that glucose fluctuation may be involved in the development of oxidative stress and vascular injury
Why This Study Is So Important

- Type 2 diabetes
  - Oxidative stress not related to A1C, fasting glucose, fasting insulin, mean blood glucose
  - Stronger correlation of oxidative stress to MAGE than to postprandial glucose levels
  - MAGE = both the ups and the downs of blood glucose
Measuring Oxidative Stress

- Nitrotyrosine: marker for peroxynitrite, a powerful oxidant increased with hyperglycemia
- 8-hydroxydeoxyguanosine (8-OHdG): a sensitive indicator of oxidative damage to DNA
- Reactive oxygen species generation by leukocytes
- “A1C of oxidative stress”
- Urinary isoprostanes: best marker of oxidative stress in total body
- Urinary 8-iso-PGF2-alpha: most common isoprostane
Oxidative Stress Marker Measurements

**Nitrotyrosine (7 days)**
- No inhibitor
- BIMI-I
- LY379196
- Mannitol
- MnTBAP

**Nitrotyrosine (14 days)**
- No inhibitor
- BIMI-I
- LY379196
- Mannitol
- MnTBAP

**80HdG (7 days)**
- No inhibitor
- BIMI-I
- LY379196
- Mannitol
- MnTBAP

**80HdG (14 days)**
- No inhibitor
- BIMI-I
- LY379196
- Mannitol
- MnTBAP

Correlation Between Urinary 8-iso-PGF2 alpha (stress marker) and MAGE in T2DM

Glycemic variability A Link between Diabetes and Cardiovascular Disease?

• Glycemic variability increases:
  – Oxidative Stress leading to endothelial damage
  – Dyslipidemia
  – Glycated Albumin
  – Hypoglycemia

Glycemic variability: A strong independent predictor of mortality in critically ill patients

Increments of mean glucose level is subdivided into four quartiles of glycemic variability. Q1 represents the lowest quartile; Q4 represents the highest quartile.

Crit Care Med 2008 Vol. 36, No. 11
Glucose variability: associated with cognitive impairment

- In 121 patients with type 2 diabetes (mean age 78 years), MAGE was associated with cognitive impairment independently of HbA1c, FPG and PPG

![Graph showing correlation between MAGE and MMSE score](image)

$r=0.83$

$p<0.001$

![Graph showing correlation between MAGE and composite score](image)

$r=0.68$

$p<0.001$

MMSE, mini-mental state examination; PPG, postprandial plasma glucose

Rizzo et al. Diabetes Care 2010;33:2169–74
Glucose Fluctuations & CVD

• Higher glucose variability is associated with increased lipid and decreased fibrous contents with larger plaque burden.

• Suggesting glycemic variability as one of the important factors related to coronary plaque vulnerability.
Glucose Variability & CAD

Cardiovascular Diabetology 2011, 10:19
GLYCEMIC VARIABILITY IS THE PREDICTOR OF HYPOGLYCEMIA
Taking a Step Back: GV Includes Hypoglycemia

- Hypoglycemia is more complicated than neuro-cognitive changes and cardiac arrhythmias (both of which can be fatal)
Hospital Admissions for Hypoglycemia Now Exceed Those for Hyperglycemia in Medicare Beneficiaries

Rita F. Redberg, MD, MSc

JAMA Internal Medicine  Published online May 17, 2014

We were pleased to read the recent Centers for Disease Control and Prevention report¹ that myocardial infarction, stroke, and hyperglycemia rates have been reduced for beneficiaries. In fact, there were 40% more admissions for hypoglycemia than for hyperglycemia over the 12-year period. The 1-year mortality rate after a hypoglycemia

Severe Hypoglycemia Identifies Vulnerable Patients With Type 2 Diabetes at Risk for Premature Death and All-Site Cancer: The Hong Kong Diabetes Registry

Alice P.S. Kong,¹ Xilin Yang,¹,² Andrea Luk,¹,³ Ronald C.W. Ma,¹ Wing Yee So,¹ Risa Ozaki,¹ Rose Ting,¹ Kitty Cheung,¹ Chung Shun Ho,⁴ Michael H.M. Chan,⁴ Chun Chung Chow,¹ and Juliana C.N. Chan¹,³,⁵,⁶
Hypoglycemia in T1DM & T2DM

• With regard to prediction of hypoglycemia, glucose variability has been shown predictive of severe hypoglycemia in T1DM and of non severe hypoglycemia in T2DM

Hypoglycemia Increases Cytokines


Hypoglycemia

Hyperglycemia
Hypoglycemia is dangerous

Review article, 2013, vol:17(5), pg: 819
Glucose Thermometer

Based on Cryer et al.
Why Nocturnal Hypoglycemia is So Dangerous

N = 25 insulin-treated patients with T2DM

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incident Rate Ratio</th>
<th>95% CV</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>8.42</td>
<td>1.40-51.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Atrial Ectopy</td>
<td>3.98</td>
<td>1.10-14.40</td>
<td>0.04</td>
</tr>
<tr>
<td>PVC</td>
<td>3.06</td>
<td>2.11-4.44</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Complex PVC</td>
<td>0.79</td>
<td>0.22-2.86</td>
<td>NS</td>
</tr>
</tbody>
</table>

Diabetes 2014;63:1738-47
Hypoglycemia, a Key GV Component, Predicts Micro and Macrovascular Complications

NEJM 2010;363:1410
Ambulatory Glucose Profile (AGP)

Decoding Dysglycemia
CGM Indications

- Indicated for use in addition to SMBG for the purpose of improving glycemic control
- Supported by ADA and AACE Guidelines for glucose monitoring
- To identify and aid in management of glycemic patterns not recognized with typical SMBG
- To prevent glycemic excursions:
  - hypoglycemia
  - hyperglycemia
CGM Indications contd.

- Glycemic variability
- Hypoglycemia
- Hypoglycemia unawareness
- Gastroparesis
- Preconception
- Behavior modification
- Insulin-requiring DM
- Evaluation of drugs – predicts complications LOS and mortality

CGM Limitations

- Technology that can’t be used to dose insulin
- All dosing decisions should be based on SMBG
- No replacement for glucose meter
- Not a Device to put and forgotten
  - Studies have shown a correlation between the number of times you look at the receiver and greater reduction in A1c
- System that doesn’t replace substitute for already existing diabetes management tools
CGM Supports Patients in Proactive vs. Reactive Self-Management

- Helps to warn of impending hypoglycemia or hyperglycemia
- Alerts/alarms help patient “stay between the lines”
- Helps detect nocturnal events
- Helps provide immediate feedback re: how changes in diet, exercise, stress, and insulin affect glucose levels
- May help avoid overreaction and/or overtreatment of high or low glucose values by alerting to impending highs and lows
- Supports pattern management
- Tracking/trending provide series of multiple sequential glucose readings over time, can aid in diabetes self-management decisions
Real Time Continuous Glucose Monitoring (CGM) Systems

Abbott FreeStyle Navigator®

DexCom™ SEVEN® PLUS

Medtronic Paradigm® REAL-Time Revel™*

*Medtronic Guardian® REAL-Time also available.

How to use the FreeStyle Libre System

1. Apply sensor with applicator

2. Scan sensor using FreeStyle Libre Reader

3. Get reading on the reader
<table>
<thead>
<tr>
<th>CGM Comparisons</th>
<th>Recommended use</th>
<th>Age approved</th>
<th>Real time vs. blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexcom 7 Plus</td>
<td>7 day</td>
<td>≥18</td>
<td>RT</td>
</tr>
<tr>
<td>Dexcom G4</td>
<td>7 day</td>
<td>≥18</td>
<td>RT</td>
</tr>
<tr>
<td>LibrePro</td>
<td>14 day</td>
<td>≥18</td>
<td>Blinded</td>
</tr>
<tr>
<td>MM Guardian</td>
<td>3 day</td>
<td>≥7</td>
<td>RT or blinded</td>
</tr>
<tr>
<td>MM IPro</td>
<td>3 day</td>
<td>≥7</td>
<td>Blinded</td>
</tr>
</tbody>
</table>
Our Experience of AMBG

Total number of patients = 35 (34 patient Type 2 DM and 1 patient Type 1 DM)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-35</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>36-51</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>52-67</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>68-83</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hba1c</strong></td>
<td><strong>6.4% to 12.4%</strong></td>
<td></td>
</tr>
</tbody>
</table>
Use of AMBG in 35 Patients

1. Evaluate glycemic variability

2. Assess periods of hypoglycemia and hypoglycemia unawareness

3. Therapeutic and lifestyle interventions

4. Highlighting variability – a major risk factor – normal HbA1c
Ms. K (Type 1 DM)
Age 18 years
HbA1c 10.8
### Daily Patterns with glucose readings
28 May 2015 - 31 May 2015 (4 days)

<table>
<thead>
<tr>
<th>Daily Average</th>
<th>Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>137</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (00:00)</th>
<th>89</th>
<th>119</th>
<th>142</th>
<th>139</th>
<th>176</th>
<th>93</th>
<th>114</th>
<th>109</th>
<th>133</th>
<th>202</th>
<th>207</th>
<th>122</th>
</tr>
</thead>
</table>

**Target Range:**
- **Low:** 70 mg/dL
- **High:** 160 mg/dL

Graph showing daily glucose levels with target range highlighted.
Daily Glucose Summary
28 May 2015 - 31 May 2015 (4 days)

Ms. K

Average Glucose
Time In Target
Time Below Target
Time Above Target

Thu 28 May
166 mg/dL
50%
4%
46%

Fri 29 May
122 mg/dL
74%
9%
17%

Sat 30 May
129 mg/dL
70%
7%
23%

Sun 31 May
131 mg/dL
42%
22%
36%

137 mg/dL
59%
11%
30%
Mr. AK
HbA1c 11 with medication changed to 6.4
Mr. P
Poor controlled diabetes
Mr. P
Increase in dosage of medicine and lifestyle measures
AGP is a visual report that collapses all glucose readings from several days or weeks as if they occurred in a single 24-hour period making it easier to visualize glycemic patterns*.

AGP graph is built from glucose readings, ideally 14 days.

* Mazze RS. Making sense of glucose monitoring technologies from SMBG to CGM. *Diabetes Technology and Therapeutics* 2005;7(5):784-7
The AGP 14-day Profile

AGP graphs contain five curves:

- **Median curve** (50th percentile) shows the median glucose value for every time point.
- The IQR shows the daily, nightly and post-prandial span of 50% of glucose values.
- Glucose variability exists when glucose values are widely spread, as indicated when the IQR and 10th and 90th percentile curves cover a large area.
The key benefits of the 14-day AGP graph
For HCPs and Patients

Benefits for HCPs

- The 14-day AGP graph clearly shows patterns in glucose levels which enables HCPs to more quickly detect potential problems, such as hypoglycemia and glucose variability.
- The AGP graphs provide the information that HCPs need to assess and fine tune therapy.

Benefits for Patients

- The information in the AGP graph is presented in a simplified way that makes it easy to understand.
- The AGP graph provides a link between day-to-day behavior and glucose levels.
“Wider use of real-time CGM in clinical practice would provide the required monitoring tool to minimize glycemic variability and superoxide overproduction. In the midst of a global diabetes epidemic, efforts to assess and minimize glycemic variability as a risk factor independent of HbA1c may help reduce the staggering burden of diabetic complications”.

CONCLUSION

• Glucose variability indicators describe the glucose profile of diabetic patients and identify any worsening glycemic control (typical of long standing diabetes) more accurately than HbA1c.

• Glucose variability is a better predictor for hypoglycaemia compared with HbA1c.

• Glucose variability is associated with oxidative stress, cognitive impairment and long-term diabetes outcomes.

• Targeting glycemic variability may help the management of diabetes better than HbA1c.

• A novel and useful parameter to predict diabetic complications, such as vascular, hyper/hypoglycemia, in diabetic population.
Thank you