A1c and Estimated Average Glucose: From Diagnosis to Management

Where Do We Stand in 2011?

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American Diabetes Association

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Disclosure - Duality of Interest

- **Research committees and grant support**
  - HealthPartners (MN), National Kidney Foundation

- **Consultant, Advisory Board, or Educational Activity**
  - Sanford – Burnham Medical Research Institute and the Florida Hospitals (TRI)
  - Streilitz Diabetes Center – Oregon Health and Sciences University

- **Employment**
  - Spouse current employee of Genentech (Roche)

The views and opinions presented herein are my own, and do not necessarily reflect the official position of the *American Diabetes Association*. All research, educational and consulting activities are performed under contract to the *American Diabetes Association Research Foundation*. Dr Kendall receives no personal or direct compensation for these activities.
Diabetes and CVD: Impact of Other CVD Risk Factors

• Diabetes Burden
  – Trends in prevalence, cost and health care burden
  – The case for early detection

• Diabetes Diagnosis and Treatment Targets
  – Using A1C for Diagnosis (2010 Standards of Care)
  – Screening for diabetes and pre-diabetes
  – Implications for prevention

• A1C and Estimated Average Glucose (eAG)
  – What’s all the fuss?
  – Role of A1C, eAG and self-monitored blood glucose (SMBG)
  – Practical applications
Early Detection of Type 2 Diabetes and Prediabetes

Implications for Intervention
Projecting the Future Diabetes Population Size and Related Costs for the U.S.

**Figure 2**—Projected distribution of newly diagnosed, undiagnosed, and established cases of diabetes, 2009–2034.

Huang ES. *Diabetes Care* 32:2225–2229, 2009
Projecting the Future Diabetes Population
The Imperative for Change

Published: 22 October 2010
Diabetes Prevention Screening For Diabetes and Pre-Diabetes

• Early detection of Diabetes and Pre-Diabetes?
  – Common clinical condition – affects 1 in 10 (1 in 5 undiagnosed)
  – Simple screening tools (risk assessment + FPG or A1C)

• Type 2 diabetes is preventable
  ▪ Diabetes risk reduced by 50% or more with lifestyle interventions
  ▪ Early intervention most effective

Harris MI. *Consultant* 1997;37(suppl):S9
The Pathophysiology of Type 2 Diabetes

- Impaired incretin effect
- Insulin resistance
- Relative insulin deficiency

Hyperglycemia
T2 diabetes and pre-diabetes

Natural History of Type 2 Diabetes
What Role Can Incretin-Based Therapy Play?

- **Glucose (mg/dL)**
- **Body weight**
- **Post-meal glucose**
- **Fasting glucose**
- **Insulin resistance**
- **Insulin level**
- **Beta-cell function**
- **Incretin effect**

A Practical Approach to Pre-Diabetes and Diabetes Prevention

Screen for Diabetes: Fasting plasma glucose (and/or OGTT)

IFG or IGT
Pre-diabetes

Lifestyle Intervention

Established Diabetes

Lifestyle plus Metformin

IFG or IGT (Pre-diabetes) plus other features*

Lifestyle Intervention and/or Metformin

Screening, Detection and Diagnosis

Identifying Higher Risk Populations

A1C for Diagnosis
Diabetes Screening and Diagnosis
ADA Criteria – Testing in Asymptomatic Adults

Testing should be considered in all adults who are overweight (BMI ≥ 25) and have additional risk factors:

- Family history of diabetes (1st degree relative)
- High risk populations group (AA, NA, Asian Am, Latino, API)
- Specific health conditions (CVD, hypertension, dyslipidemia)
- Past history of elevated blood glucose or A1C
- History of gestational diabetes or child > 9 lbs at birth
- Other conditions associated with insulin resistance
  - Morbid obesity, polycystic ovarian syndrome (PCOS), acanthosis

In the absence of risk factors, testing should begin at age 45 years. If normal, testing should be repeated at least every 3 years in a clinic setting.

American Diabetes Association. Standards of Medical Care in Diabetes – 2010
Diabetes Care 33; Suppl 1, S11-S61, 2010
Diabetes Risk – Identifying Risk
Screening Tools from the ADA and CDC
Diagnosis of Diabetes 2009

- To test for pre-diabetes or diabetes:
  - Fasting plasma glucose
  - Oral Glucose Tolerance Test (75 gm),
  - or both is appropriate.

- An OGTT may be considered in patients with impaired fasting glucose (IFG)

<table>
<thead>
<tr>
<th>NORMAL</th>
<th>PREDIABETES IFG or IGT</th>
<th>DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG &lt; 100</td>
<td>FPG ≥ 100 – 125 (IFG)</td>
<td>FPG ≥ 126</td>
</tr>
<tr>
<td>2-h PG &lt; 140</td>
<td>2-h PG 140 – 199 (IGT)</td>
<td>2-h PG ≥ 200</td>
</tr>
</tbody>
</table>

ADA Clinical Practice Recommendations, *Diabetes Care* 32 (Suppl 1), 2009
The Emergence of A1C as Diagnostic Tool

A New Look at Screening and Diagnosing Diabetes Mellitus

Christopher D. Saudek, William H. Herman, David B. Sacks, Richard M. Bergenstal, David Edelman, and Mayer B. Davidson


• Diabetes should be diagnosed when A1C is ≥6.5% (and confirmed)
• Confirmation not required if symptomatic and glucose >200 mg/dl
  – If A1C testing not possible, previously diagnostic methods (e.g., FPG or 2 hr PCG with confirmation) are acceptable

Diagnosis of Diabetes 2010-11
Simplified Screening and Detection

- **A1C ≥ 6.5%** (NGSP, DCCT* standard) – non-fasting test
  - Fasting glucose ≥ 126 mg/dl (8 hour fast)
  - 2 hour glucose ≥ 200 mg/dl during OGTT (WHO 75 g test)
- If symptoms of hyperglycemia = random glucose ≥ 200 mg/dl

<table>
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<th>PRE-DIABETES (IFG or IGT)</th>
<th>DIABETES</th>
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<td>FPG ≥ 126</td>
</tr>
<tr>
<td>2-h PG &lt; 140</td>
<td>2-h PG 140 – 199 (IGT)</td>
<td>2-h PG ≥ 200</td>
</tr>
<tr>
<td><strong>A1c &lt; 5.7%</strong></td>
<td><strong>A1c 5.7 – 6.4%</strong></td>
<td><strong>A1c ≥ 6.5%</strong></td>
</tr>
</tbody>
</table>

Use of HbA1C for Screening and Diagnosis
Pros and Cons

**Pro**
- Does not require overnight fast
  - Increased rate of screening
- Reflects long-term glycemic burden
  - Less affected by acute events, physiologic stress
  - Accepted and current guide in management of diabetes
- Laboratory methods now well standardized and reliable

**Con**
- Greater cost of individual test
  - Limited availability in certain regions
- Variable correlation between A1C and glucose testing
- Unresolved questions
  - What is the “Gold Standard” for diagnosis?
- Potential variation by population group

Use of A1C and Estimated Average Glucose in Clinical Care

The Role of Glycemic Testing
“So, Mrs. Smith, it looks like you have diabetes. Your repeat fasting blood sugar was 178, and as you recall the first one was 187. A glucose level over 126 is classified as diabetes.”

In addition we measured your hemoglobin A1c and this level was also very high at 8.6%. Normal is less than 6%. Ideally we would like to get it below 7.”
A Typical Patient Response

“Um….what’s a hemoglobin A1c…?"

“Whatever you said? I do recall that my hemoglobin level was low when I was pregnant.

“And what were those other numbers?

“What do you mean, 7%…of what?”
Let Me Diagram it For You…

\[ \frac{G}{G} = \_\% \]
The Concept of Average Glucose

• The Clinical Dilemma
  – HbA1c: useful for research, risk prediction, target of therapy
  – Well standardized measurement
  – HOWEVER, difficult to explain to patients

• Clinical Utility of HbA1C
  – We work to tell patients what the HbA1c represents…but concept of % is difficult
  – Glucose levels are familiar to patients from SMBG and lab
  – Does the HbA1c test in fact represent an average glucose?
### Historical Studies Examining Relationship Between HbA1c and Mean Glucose

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cohort</th>
<th>Study period (weeks)</th>
<th>SMBG tests/pt over 1-3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svendsen</td>
<td>1982</td>
<td>Type 1 (n=15)</td>
<td>5</td>
<td>200-300</td>
</tr>
<tr>
<td>Nathan</td>
<td>1984</td>
<td>Type 1 (n=21)</td>
<td>8</td>
<td>200-300</td>
</tr>
<tr>
<td>DCCT</td>
<td>2002</td>
<td>Type 1 (n=1439)</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Hempe</td>
<td>2002</td>
<td>Type 1 (n=128)</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>Murata</td>
<td>2004</td>
<td>Type 2 (n=182)</td>
<td>8</td>
<td>180</td>
</tr>
<tr>
<td>Nathan</td>
<td>2007</td>
<td>Type 1 (n=22)</td>
<td>12</td>
<td>24,000 (CGMS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 non-diabetes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Need for systematic study of relationship between A1C and average glucose**
Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

DM Kendall. International Diabetes Center
A1C Derived Average Glucose (ADAG) International Study:

Translating the A1C Assay Into Estimated Average Glucose Values

David M. Nathan, MD
Judith Kuenen, MD
Rikke Borg, MD
Hui Zheng, PhD

David Schoenfeld, PhD
Robert J. Heine, MD

For the A1C-Derived Average Glucose (ADAG) Study Group*
A1C Derived Average Glucose (ADAG) Study: Objectives and Study Participants

To determine the mathematical relationship between HbA1c and average glucose level

• To establish that the relationship is valid across:
  – Diabetes types
  – A wide range of HbA1c levels and age
  – Across different population groups/ethnicities

• Recruitment of:
  – Both type 1 and type 2 diabetes, as well as healthy volunteers
  – Distribution by ethnicity and HbA1c (4-6.5%, 6.6-8.5%, >8.5%)

• Exclusion criteria
  – Any condition that may interfere with measurement of A1c or glucose

A1C Derived Average Glucose (ADAG) Study: Measurements of Glycemia

- Continuous glucose monitoring
  - Calibrated by 8-point glucose profiles
- Self monitored blood glucose (7-point profiles)
  - 3 days per week
- HbA1c at baseline and monthly
  - Utilizing DCCT-aligned assay in a central laboratory

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Enrolled</td>
<td>661</td>
<td></td>
</tr>
<tr>
<td>Eliminated from analysis</td>
<td>154</td>
<td>(23%)</td>
</tr>
<tr>
<td>Dropped out or excluded</td>
<td>91</td>
<td>(14%)</td>
</tr>
<tr>
<td>Inadequate CGM</td>
<td>11</td>
<td>(2%)</td>
</tr>
<tr>
<td>Inadequate HbA1c sample</td>
<td>52</td>
<td>(8%)</td>
</tr>
</tbody>
</table>

## A1C Derived Average Glucose (ADAG) Study: Baseline Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>Non-diabetes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>268</td>
<td>159</td>
<td>80</td>
<td>507</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>43 ± 13</td>
<td>56 ± 9</td>
<td>40 ± 14</td>
<td>46 ± 14</td>
</tr>
<tr>
<td><strong>Gender (% F)</strong></td>
<td>52%</td>
<td>50%</td>
<td>69%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>93%</td>
<td>73%</td>
<td>71%</td>
<td>83%</td>
</tr>
<tr>
<td>African/Af-Am</td>
<td>2% (5)</td>
<td>13% (21)</td>
<td>15% (12)</td>
<td>8% (38)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6% (15)</td>
<td>8% (12)</td>
<td>15% (12)</td>
<td>8% (39)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pump</td>
<td>47%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td>53%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet only</td>
<td></td>
<td></td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Oral agent only</td>
<td></td>
<td></td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Insulin only</td>
<td></td>
<td></td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Insulin &amp; oral</td>
<td></td>
<td></td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

A1C Derived Average Glucose (ADAG) Study: Glucose Monitoring and Analysis

- CGM - mean of ~ 2,400 measurements per subject
- SMBG ~ mean of 300 measurements per subject
  - Mean of ~ 25 measurements/wk. goal was minimum of 21 tests per week
  - Total ~ 2,700 measurements/subject during 12 weeks
- Analysis
  - CGM results corrected by factor of 1.05
  - Glucose measure weighted in proportion to the inverse of total number of measurements on that day
  - Arithmetic mean glucose calculated for each subject
  - Linear and quadratic regression used to estimate relationship
- More than 90% of individual subjects’ AG must fall within +/- 15% of study wide calculated AG

A1C Derived Average Glucose (ADAG) Study: Results

\[
\text{Average Glucose (mg/dl)} = 28.7 \times \text{HbA1c} - 46.7
\]

\[
R^2 = 0.84, \quad P < 0.0001
\]

> 90% of cohort Values fall within ± 15%
A1C Derived Average Glucose (ADAG) Study: Other Factors Examined

Does ADAG relationship differ by:

- Type 1 or type 2 diabetes: NO
- Presence or absence of diabetes: NO
- Degree of glucose variability: NO
- Gender: NO
- Age: NO
- Smoking: NO
- Race/Ethnicity: NO

(trend toward higher HbA1c in African/AA vs. whites)
Implications and Clinical Translation

• Correlation between HbA1c and AG
  – Allows for translation of HbA1c into estimated Average Glucose (eAG)

• eAG will apply to the majority of patients with diabetes
  – Barring “traditional” conditions interfering with the assay or relationship between glucose and A1C
    ▪ Hemoglobinopathy - detectable by central lab in most cases
    ▪ Anemia – acute or active
    ▪ Pregnancy – which lowers A1C via hemodilution
    ▪ Renal failure due to formation of carbamyl-Hb
    ▪ Drugs including dapsone, erythropoietin stimulators

Clinical Use of Estimated Average Glucose Correlation with A1C

Help patients make the connection between daily and long-term glycemic control

diabetes.org/professional/eAG

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Estimated Average Glucose (eAG)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
</tr>
<tr>
<td>6.0</td>
<td>126</td>
</tr>
<tr>
<td>6.5</td>
<td>140</td>
</tr>
<tr>
<td>7.0</td>
<td>154</td>
</tr>
<tr>
<td>7.5</td>
<td>169</td>
</tr>
<tr>
<td>8.0</td>
<td>183</td>
</tr>
<tr>
<td>8.5</td>
<td>197</td>
</tr>
<tr>
<td>9.0</td>
<td>212</td>
</tr>
<tr>
<td>9.5</td>
<td>226</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>
What Won’t Change…
And What’s New

• Clinical use of A1C
  – No change in the standardized HbA1c assay
  – eAG now added as an educational tool for patients, families, and providers
  – Links SMBG to A1C values – motivates and educates patients on impact of daily blood glucose and overall glycemic control

• The “new” HbA1C assay report
  – New standardized assay worldwide implemented worldwide (2009)
  – Reporting % as currently used (DCCT values)
    ▪ IFCC units reported in mmol HbA1c/mol Hb
    ▪ eAG also reported in most laboratories (as mg/dl or mM)
# Standardizing the HbA1C Report
## The Era of IFCC and NGSP

<table>
<thead>
<tr>
<th>IFCC HbA1c (mmol/mol)</th>
<th>NGSP HbA1c (%)</th>
<th>eAG (mg/dL)</th>
<th>eAG (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>5</td>
<td>97</td>
<td>5.4</td>
</tr>
<tr>
<td>42</td>
<td>6</td>
<td>126</td>
<td>7.0</td>
</tr>
<tr>
<td>53</td>
<td>7</td>
<td>154</td>
<td>8.6</td>
</tr>
<tr>
<td>64</td>
<td>8</td>
<td>183</td>
<td>10.2</td>
</tr>
<tr>
<td>75</td>
<td>9</td>
<td>212</td>
<td>11.8</td>
</tr>
<tr>
<td>86</td>
<td>10</td>
<td>240</td>
<td>13.4</td>
</tr>
<tr>
<td>97</td>
<td>11</td>
<td>269</td>
<td>14.9</td>
</tr>
<tr>
<td>108</td>
<td>12</td>
<td>298</td>
<td>16.5</td>
</tr>
</tbody>
</table>

Resources for Estimated Average Glucose from the American Diabetes Association

• Provider education and materials
  – Scientific Sessions, Post Graduate Course and other meetings
  – eAG calculator (handheld by request and professional.diabetes.org)

• Patient education information
  – Diabetes.org
  – Diabetes Forecast, pamphlets and brochures

diabetes.org/living-with-diabetes/treatment-and-care
professional.diabetes.org/GlucoseCalculator.aspx
Resources for Estimated Average Glucose from the American Diabetes Association

diabetes.org/living-with-diabetes/treatment-and-care
professional_diabetes.org/GlucoseCalculator.aspx
A Typical Patient Encounter circa 2011

“So, Mrs. Smith, it looks like you do have diabetes. Your average blood sugar is around 200. When people don’t have diabetes, this number is below 125.

We need to work with you to try to get this number, the average glucose, down below 150 over the next few months with some weight loss, exercise, and a medication. Let’s talk some more about what you can do…”
Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

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