Diagnosing and Managing Diabetes: Beyond the Guidelines

Dr. Shadi Tabba
Consultant Pediatric Endocrinologist
Dubai Diabetes Center / Dubai Health Authority
Disclosures

- I have no industry relations or conflicts of interest to disclose.
Objectives

- Knowing the diagnostic criteria for Diabetes and their challenges
- Understanding the pitfalls in making the diagnosis
- Learning how to select the right screening tool for Diabetes
- Understanding the different tools used to monitor Diabetes control
Diagnosing Criteria for Diabetes Mellitus

- **FPG ≥126 mg/dL (7.0 mmol/L)**
  Fasting is defined as no caloric intake for ≥8 hours

- **2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)**
  Using glucose load: 75g anhydrous glucose dissolved in water (kids?)

- **A1C ≥6.5% (48 mmol/mol)**
  *In lab using NGSP-certified method & standardized to DCCT assay*

- **Random PG ≥200 mg/dL (11.1 mmol/L)**
  In individuals with symptoms of hyperglycemia or hyperglycemic crisis

Standards of medical care in diabetes.
*Diabetes Care.* 2016;39(suppl 1):S1-S106
## Diagnosis of DM on OGTT

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>2 Hour PP</th>
<th>Any Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>&lt; 100</td>
<td>&lt; 140</td>
<td></td>
</tr>
<tr>
<td>IFG/ IGT (Borderline DM)</td>
<td>100-125</td>
<td>140-199</td>
<td></td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td>≥ 126</td>
<td>≥ 200</td>
<td>≥ 200 with symptoms</td>
</tr>
</tbody>
</table>

These figures were based on big studies which showed them to be numbers when risk of long-term complications are higher.

If both IFG and IGT it is called IGT. No change in approach for that.

Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010 Jan. 33 Suppl 1, S62-69
Diagnosis of DM on OGTT: Challenges

- OGTT needs special preparation which is sometimes missed:
  1- Fasted 8-14 hours (? up to 16 hours). Water allowed.
  2- Between 7 and 9 a.m.
  3- On the 3 previous days, needs to have eaten ≥150 g carbs/day
  4- Patient not sick with acute illness which may raise the readings. Stress and exercise may affect it too.
  5- If already on medication (oral hypoglycemics or insulin)
Diagnosis of DM on OGGT: Challenges

- OGGT has high individual variability among people in general and also among different ethnicities (less so with FPG alone). Inter-individual variation 12.5%.

- OGGT results are poorly reproducible (less so with FPG) due to factors like illness, diurnal variation, stress, exercise. Intra-individual variation 5.7%-8.3%.

- OGGT is inconvenient for the patient and costly (less so with FPG)

- Even though the numbers for borrowed as-is for use in diagnosing diabetes in kids, no firm proof supports this


Diagnosis of DM on OGGT: Challenges

- Discussions about whole blood vs. plasma vs. serum glucose.
- Whole blood measure will vary based on Hct.
- Plasma vs. Serum: Studies did not agree.
- Spin or freeze sample as glycolysis continues 5-7% decrease glucose per hour. Adding Fluoride only works 4 hours after addition.
- Capillary sample vs. IV drawn: Capillary glucose concentrations can be 20–25% higher during an OGGT and will also vary based on Hct.


Diagnosis of DM on OGTT: Challenges
Diagnosis of DM on OGTT: Challenges

- Even FPG has many of the same issues

- NHANES III: 685 fasting non diabetic adults: Only 70.4% of people with FPG ≥126 mg/dL on the first test had FPG ≥126 mg/dL when analysis was repeated ~2 weeks later.

Diagnosis of DM by HgbA1c: Advantages

- Test obtainable anytime of day, no need for fasting
- Whole blood is fine
- Assay is amenable to standardization
- Represents long term glucose, so not affected by acute factors
- Level proven to correlate and represent long term complications
Diagnosis of DM by HgbA1c: Challenges

- HgbA1c is an indicator for hyperglycemia over time. Recent development of diabetes may not show as abnormal A1c.

- HgbA1c measurement needs to be very accurate, and so the method used by the lab needs to be “National Glycohemoglobin Standardization Program” certified.

- There are factors that affect how representative HgbA1c is for the presence of diabetes:
Factors Affecting HgbA1c

- Race/ Ethnicity, unclear if true, but no different range for races yet
- Erythropoieses:
  Increase in iron or B₁₂ deficiency, Decrease in treatment or liver disease
- Altered Hgb: Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF and methemoglobin may increase or decrease HbA₁c either affecting RBC lifespan or glycation
- Glycation:
  Increased HbA₁c: alcoholism, chronic kidney disease
  Decreased HbA₁c: aspirin, vitamin C and E, HyperTG-emia
- RBC lifespans:
  Increase A₁c w/ increased lifespan as in splenectomy
  Decrease A₁c w/ decreased lifespan: Hgbpathy, Splenomeg, CKD/ HD
How Should We Diagnose Diabetes???
How Should We Diagnose Diabetes???

- Knowing and understanding the different tests we can use and the pitfalls of each (FPG, OGTT, Random BG, 2-hr PPG, HgbA1c).

- Accordingly, use clinical sense to choose the test to do.

- Some patients will have clear-cut result (e.g. symptomatic patient with random BG of 300 and HgbA1c of 10%), no need for OGTT.

- Others will need clinical judgement, combination or repeat of tests to get an answer.
Other Tools for Glucose Assessment
Glycated Albumin

- Use for diagnosis: not common

- HgbA1c is the test which has been studies and physicians are used to

- HgbA1c is the one who has been more extensively used in studies with clear understanding of different A1c levels and their association with good control vs. long term complications (e.g. DCCT). Despite some small studies, no long-term, large-scale clinical trials have investigated the use of glycated albumin as an indicator of glycemic control.

Glycated Albumin

- A ketoamine formed from glycation of Albumin

- **Indicator for glucose level in the previous 2-3 weeks**

- **Not affected by Hgbopathy**

- **Not affected by CKD/ HD**


- **Slight effect of age, BMI, WC (all inversely), and of course liver disease**
Glycated Albumin

- Suggested use in diagnosis in combination with FPG to decrease need for OGTT in borderline cases

- Using FPG < 100 and GA < 14% to exclude diabetes and FPG ≥ 126 and GA ≥ 17 as diagnostic for diabetes had a sensitivity of 83.3% and specificity of 98.2% but there was still need for OGTT to confirm diagnosis in 35% of cases.

- When exclusion of diabetes was switched to GA < 15%, sensitivity was 85.6%, specificity was at 98.2%, and OGTT rate of 22.5%.

Glycated Albumin

- Use of GA in monitoring a known diabetic:

Glycated albumin may be used in patients with known anemia, hemoglobinopathy, chronic kidney disease, or on hemodialysis, to assess diabetes control rather than use of HgbA₁c (unless they have heavy protein loss or they are on peritoneal dialysis)

It reflects the prior 2-3 weeks, so it can (theoretically) be used to assess improvements in diabetes control after change in insulin settings or introduction of new medications

Yet unknown at what stage of kidney disease it becomes better than A₁c
The relationship between serum glycated albumin, hemoglobin A1c, fasting plasma glucose, and plasma glucose 2h after oral glucose tolerance test.

<table>
<thead>
<tr>
<th>Serum GA (%)</th>
<th>Hemoglobin A1c (% mmol/mol)</th>
<th>FPG (mg/dL, mmol/L)</th>
<th>OGTT 2h PG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>5.6 (38)</td>
<td>89 (5.0)</td>
<td>114 (6.3)</td>
</tr>
<tr>
<td>14</td>
<td>5.7 (39)</td>
<td>92 (5.1)</td>
<td>125 (7.0)</td>
</tr>
<tr>
<td>15</td>
<td>5.9 (41)</td>
<td>96 (5.3)</td>
<td>137 (7.6)</td>
</tr>
<tr>
<td>16</td>
<td>6.1 (43)</td>
<td>99 (5.5)</td>
<td>149 (8.3)</td>
</tr>
<tr>
<td>17</td>
<td>6.3 (45)</td>
<td>104 (5.8)</td>
<td>162 (9.0)</td>
</tr>
<tr>
<td>18</td>
<td>6.5 (48)</td>
<td>108 (6.0)</td>
<td>175 (9.7)</td>
</tr>
<tr>
<td>19</td>
<td>6.7 (50)</td>
<td>113 (6.3)</td>
<td>189 (10.5)</td>
</tr>
<tr>
<td>20</td>
<td>6.9 (52)</td>
<td>118 (6.6)</td>
<td>203 (11.3)</td>
</tr>
<tr>
<td>20.5</td>
<td>7.0 (53)</td>
<td>121 (6.7)</td>
<td>210 (11.7)</td>
</tr>
<tr>
<td>21</td>
<td>7.1 (54)</td>
<td>124 (6.9)</td>
<td>218 (12.1)</td>
</tr>
<tr>
<td>22</td>
<td>7.4 (57)</td>
<td>130 (7.2)</td>
<td>233 (12.9)</td>
</tr>
<tr>
<td>23</td>
<td>7.7 (61)</td>
<td>136 (7.5)</td>
<td>248 (13.8)</td>
</tr>
<tr>
<td>24</td>
<td>7.9 (63)</td>
<td>143 (7.9)</td>
<td>265 (14.7)</td>
</tr>
<tr>
<td>25</td>
<td>8.2 (66)</td>
<td>150 (8.3)</td>
<td>281 (15.6)</td>
</tr>
<tr>
<td>26</td>
<td>8.5 (69)</td>
<td>157 (8.7)</td>
<td>298 (16.6)</td>
</tr>
<tr>
<td>27</td>
<td>8.8 (73)</td>
<td>165 (9.1)</td>
<td>316 (17.5)</td>
</tr>
<tr>
<td>28</td>
<td>9.2 (77)</td>
<td>173 (9.6)</td>
<td>334 (18.5)</td>
</tr>
<tr>
<td>29</td>
<td>9.5 (80)</td>
<td>181 (10.1)</td>
<td>352 (19.6)</td>
</tr>
<tr>
<td>30</td>
<td>9.8 (84)</td>
<td>190 (10.6)</td>
<td>371 (20.6)</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose; GA, glycated albumin; OGTT 2h PG, plasma glucose 2 hours after oral glucose tolerance tests.

doi:10.1371/journal.pone.0146780.t002

Fructosamine

- Like GA, it is a measure of glucose concentration in the previous 2-3 weeks.

- Current method for measuring GA is also better standardized and less vulnerable to preanalytical variables than those used for Fructosamine.

- It is also a measure of glycated proteins (including albumin) which like GA is not affected by Hgbopathy and anemia but may be affected by conditions causing protein/albumin loss, and thyroid disorders.

- $\text{HgbA1c} = 0.017 \times \text{Fructosamine} + 1.61$

- Vitamin C supplements interfere with the assay

- General agreement that it is not a good screening test, but may have a role in monitoring as in GA.
<table>
<thead>
<tr>
<th>Glucose (mg/dl)</th>
<th>Fructosamine (umol)</th>
<th>A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>212.5</td>
<td>5.0</td>
</tr>
<tr>
<td>120</td>
<td>250</td>
<td>6.0</td>
</tr>
<tr>
<td>150</td>
<td>287.5</td>
<td>7.0</td>
</tr>
<tr>
<td>180</td>
<td>325</td>
<td>8.0</td>
</tr>
<tr>
<td>210</td>
<td>362.5</td>
<td>9.0</td>
</tr>
<tr>
<td>240</td>
<td>400</td>
<td>10.0</td>
</tr>
<tr>
<td>270</td>
<td>437.5</td>
<td>11.0</td>
</tr>
<tr>
<td>300</td>
<td>475</td>
<td>12.0</td>
</tr>
<tr>
<td>330</td>
<td>512.5</td>
<td>13.0</td>
</tr>
<tr>
<td>360</td>
<td>550</td>
<td>14.0</td>
</tr>
<tr>
<td>390</td>
<td>587.5</td>
<td>15.0</td>
</tr>
</tbody>
</table>
1,5-anhydroglucitol

- A monosaccharide found in almost all foods.

- Remains stable in levels in normal person. Whatever is ingested is equal to what is excreted in the urine.

- While all passes out of the glomerulus, most is absorbed back.

- When glucose is over 180 mg/dl, and the kidneys can’t reuptake all of it back, there is competition with the 1,5-anhydroglucitol reuptake leading to more loss of it in the urine. This leads to drop in 1,5-AG levels.

- As glucose levels drop and normalize over time, 1,5-AG levels rise back to normal.

1,5-anhydroglucitol

- Seems to be a more short-term measure of glucose control as any post prandial rises in glucose in the last 2 weeks can decrease its level. So it’s good to indicate postprandial excursions.

- Thus, it may be more useful in patients with generally better control at or under HgbA1c of 8% to assess post prandials like T1DM kids.


- Inaccurate in patients with liver disease or renal failure, and obviously inaccurate in patient on SGL-2 inhibitors, but unaffected by the things affecting HgbA1c.

- It is however unlikely that 1, 5-AG could replace A1C and there are few data or studies to indicate that the test reflects risk of microvascular or macrovascular complications. There is high racial disparity.

  McGill, J. et al; Diabetes Care 27(8): 1859-1865; 2004
  Herman, W. et al; JCEM 94(5): 1689-1694; 2009
# 1,5 AG vs. Average PPG

<table>
<thead>
<tr>
<th>1,5- AG (GlycoMark) (µg/mL)</th>
<th>Approximate Mean Postmeal Maximum Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 12</td>
<td>&lt; 180</td>
</tr>
<tr>
<td>10</td>
<td>185</td>
</tr>
<tr>
<td>8</td>
<td>190</td>
</tr>
<tr>
<td>6</td>
<td>200</td>
</tr>
<tr>
<td>4</td>
<td>225</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>&gt; 290</td>
</tr>
</tbody>
</table>
Despite its flaws, we return to HgbA1c as the indicator and test most frequently used to monitor glucose control in our diabetics.

We also download and assess SMBG’s which patients detest.

But until when?
The Problem with A1c (and SMBG)

HgbA1c 7%

The Many Faces of a 7% A1c

Time spent

1. HIGH: 24%
2. IN RANGE: 29%
3. LOW: 8%

1. IN RANGE: 58%
2. LOW: 18%
3. HIGH: 63%

1. LOW: 100%
Alternative to A1c

- As more people use some form of CGMS, we need to transition towards a better tool

- Time in range as a percentage, now used extensively as a measure of diabetes control in closed loop / AP studies

- Still A1c in studies submitted to regulating bodies. Why? Classic studies, CGMS price