Pros and Cons of HbA1C in the diagnosis of Diabetes Mellitus

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- Diadetes mellitus:It’s a clinical syndrome chatacterised by hyperglycemia due to absolute or relative deficiency of insulin.
- *Diagnostic Criteria of DM*:
  - A1C >/= 6.5%.or
  - FPG >/= 126mg/dl (7.0 mmol/L) or
  - 2hr Plasma glucose >/=200mg/dl(11.1mmol/L)or
  - Classic symptoms of hyperglycemia or hyperglycemic crisis,Random PG>=200mg/dl(11.1mmol/L)

- *Glycated Hb*:

  Nonenzymatic condensation of glucose to N-terminal valine of Beta chain of Hb.

- 1% increase HbA1C ~2mmol/L(36mg/dl)BG.
- An international expert committee convened in 2008 by ADA,EASD and IDF focused to consider HbA1C for DM dianosis as an alternative but not superior to blood glucose.

PROs of HbA1C

- A1C captures chronic hyperglycemia better than two assessment of FPG or 2hrOGTT.

- ✓ FBS &2hr OGTT just a moment of a single day!
- ✓ A1C measurement equals the assessments of hundreds of FBS level,also Postprandial peaks.
- ✓ i.e.Serum IGF-1 is definitely more efficacious than S.Growth hormone to monitor Acromegaly.

❑ A1C better associated with chronic complications than FPG

✓ Macrovascular complication like CVD in DM is 5-10folds higher and association of A1C with CVD is remarkable.

✓ Nonproliferative Retinopathy increases at A1C around 6.5%.

In General,FPG is poor marker for future complication like CVD.

❑ Fasting not needed for A1c and no acute perturbations affect it.

- ✓ Acute stress >increase endogenous glucose production &impair glucose utilization.
- ✓ Morning exercise may affect FBG.

❑ A1C –greater pre-analytical stability

- ✓ Blood collection tube may not contain anti glycolytic substance.
- ✓ Even do,glucose consumption occurs in blood cells in frist 1-2hr after sampling.

- ✓ Glucose conc.reduced 5-7%(~ 0.5 mmol/L/Hr)and higher in hot weather.
- ✓ So,DM diagnosis may be missed!
- ✓ Pre-analytical variability of FPG is 5-10%, whereas A1C being ~2%.

❑ Standardization of A1C assey isn't inferior to glucose assey

- ✓ Survey in 6000 in USA lab.documented significant bias in *glucose* assesment in as many as 41%
- ✓ Misclassification *of glucose tolerence* in 12%.
- ✓ A great effort was made in USA to make reproducable A1Cto minimise lab.biases and to use it for monitoring as well as for DM diagnosis.

❑ Biological variability is lower than that for FPG.

- ✓ Biological variability is several fold lower than FPG(<1 vs.~ 4%).
- ✓ Co-efficient of variation of A1C:FPG:2hr PG- 3.6: 5.7 : 16.6%

❑ Individual susceptibility to glycation might be an additional benefit of A1C assessment.

- ✓ Subject with high HGI-->greater retinopathy ,nephropathy risk *even with good glucose control*→also possess susceptibility to protein glycation.

- A1C-same biomarker for diagnosing and monitoring of DM-advantage.

✓ Subject with A1c >6.5%(diabetic)- baseline measured and deviation from target available.

A1C 6.0 -6.49%(High risk)- start effective prevention strategy.

A1C 5.50- 5.99% + other diabetic risk factors – counselling offered.

Reasons to prefer HbA1C to diagnose DM

- Ch.hyperglycaemia captured.
- A1C is better related to CVD than FPG.
- Fasting not needed for A1C.
- No acute perturbation(stress,diet) affect A1c.
- Greater preanalytical stability.
- Biological variability is lower.

- Susceptibility to protein glycation may be caught by A1C.

- Used for diagnosing and also monitoring of DM.

Cons of HbA1C for diagnosis of DM

- DM defined by high blood sugar: not by protein glycation.
  - ✓ A1C certainly secondary to elevated blood glucose but there is some delay –might have negative clinical consequences.

- A1C is poor marker of important pathophysiological abnormalities featuring DM.

- ✓ **A1**C capture only chronic hyperglycemia but not the acute state,as like ABPM(ambulatory BP Monitoring correlates more with CV events by daily variation of BP.

- ✓ **IRAS** shows weaker relation of A1C *to insulin resistance and secration than FPG,2Hr PG.*

- A1C-poor sensitivity for DM diagnosis.
  - ✓ It misses large proportion of asymptomatic early DM that can be detected by OGTT.
  - ✓ Recent chinese study,A1C sensitivity less than FPG.
- Impact on Epidemiological studies.
  - ✓ A1C >6.5%identify ~30-40% of previously undiagnosed DM.But FPG~50%:2hr PG~90%.

- ✓ In IRAS-this figure is for HbA1C,FPG,2hr PG is 30%,46%,and 90% repectively.

- ✓ In chinnai study,A1C >6.5%detect 78% of newly diagnosed DM.

❑ 2hr PG & IGT stronger predictor for DM.

- ✓ High glucose is toxic for tissue damage.So,FPG is poor marker than 2hr.PG &A1C.

- ✓ In a study of retinopathy of pima indians,ADA reported IGT have ~40%increased mortality than normoglycemia&this *can't be* diagnosed by FPG or A1C.

- Standerdization of A1C assey is poor rather glucose assey is easier to implement.
- A1C assey is unreliable &cant be used in many subjects.
  - ✓ Several conditions (like malaria,ch.anaemia,major blood loss,uremia,pregnancy,smoking,infection) may influence the A1C resault.

- Within day-biological variability of plasm glucose cant be rejected.
- A1C may be misinterpritated.
  - A1C may be falsely low in:
    - High RBC turnover.
    - Taking iron,vit B 12.or any such product
    - Blood transfusion in last 3months

- A1C may be falsely high in:

  - Iron deficiency anemia.
  - VitB 12/folate deficiency.
  - Alcoholism or CKD.
  - Hb.pathies: sickel cell anemia,methamoglobinemia.

- Individual susceptibility to glycation of Hb isn't relevant to DM diagnosis.
  - ✓ High HGI has greater risk of developing retinathy & nephropathy even when they had good glucose control.
  - ✓ A1C reflects high mean exposure to glucose but not flactuation during day.

- Using same biomarker for monitoring & diagnosis *may not have* positive effect.

✓ 6.5% A1C threshold misses a large percentage of previously undiagnosed DM.

✓ In Finnish Diabetes prevention study,sensitivity of A1C>6.5% to diagnosisDM only 39%:

i.e.61% newly diagnosed case had A1C<6.5%

Reasons not to prefer A1C for DM diagnosis:

- It's the glycation of protein rather direct blood glucose.
- A1C has poor sensetivity to diagnosis & would change epidemiology of diabetes.
- Fasting isn't essential to identify perturbation in glucose metabolism.

- Standardization may be poor ,even in western countries.
- Individual susceptibility to glycation of Hb isn't relevant to DM diagnosis.
- Using the same biomarker for diagnosing and monitoring might have negative effect.
- Cost of A1C is much higher.

- A1C levels vary not only to glycemia ,but also to erythrocyte turnover rates & others.
- A1C levels 6.0-6.5% don't predict DM effectively as FPG& OGTT.
- Sensitivity of A1C to detect DM defined by OGTT is < 50%;so,majority of DM will remain undiagnosed if A1C is used.

- No Diabetes prevention trail s have selected their populations based on A1C.
- Using A1C may delay the diagnosis in ~60% of incident case.

We agree that the research and debate on pros and cons of using A1C vs glucose assey as diagnostic tool for DM should continue in a constructive manner until a larger and truly evidence based consensus is reached,

Thank you very much